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THIOCYANATE IN HYPERTENSION

BLOOD PRESSURE BEHAVIOR AFTER WITHDRAWAL OF THE DRUG, AND SERIAL ELECTROCARDIOGRAMS AS CRITERIA OF RESPONSE

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SYMPTOMATIC improvement and blood pressure drop in 60 to 80 per cent of thiocyanate-treated hypertensive patients, as found by Barker[1] in 1936, and confirmed by numerous other workers, appeared to be present in a comparable series published by one of us (E.J.F.) five years ago.[2] Continued observation since the appearance of that paper revealed, that in many patients, blood pressure rise and relapse of symptoms did not follow withdrawal of the drug. The justification of ascribing improvement to thiocyanate in these cases seems doubtful, as does also the comparison of *initial* blood pressure readings with after-treatment values as a measure of response to the drug. Claims regarding the depressor effect of numerous treatment measures[3-6] were supported by initial control alone, and remained unconfirmed. Of sixteen papers reporting favorably on thiocyanate, no control period is mentioned in eight; in six, an initial thiocyanate-free period is used as a control and in only two are alternating courses of a placebo employed.[7,8]

In the following, thiocyanate action is re-examined, taking blood pressure rise after withdrawal as the criterion of response. To obtain an objective measure of progress, electrocardiograms were recorded serially. A nonthiocyanate-treated control series is also included.

MATERIAL AND METHOD

Fifty thiocyanate-treated patients and thirty-six patients who did not receive the drug were studied. Of the first group all but ten were women. All were ambulatory. Ages ranged from 27 to 76. The systolic blood pressure ranged from 180 to 260 mm. Hg, the diastolic from 100 to 140 mm. of mercury. Two were patients with malignant hypertension.

A full course of observation consisted of an initial placebo period of 4 to 12 weeks, a thiocyanate treatment period of 12 to 156 weeks, and a terminal placebo period of 4 to 12 weeks. The mean systolic and diastolic pressures

obtained from weekly measurements, in each of the three phases, were compared, omitting the first measurement in the first phase, and discarding measurements taken before adjustment of the dose and stabilization of the blood thiocyanate level, in the second phase. In the third phase measurements commenced after the return of the blood thiocyanate level to normal, and not less than eight weeks after cessation of thiocyanate administration. The blood pressure was measured throughout under comparable conditions and by the same observer.

The blood thiocyanate level was not allowed to exceed 14 mg. per cent. The placebo consisted essentially of a flavoring, which was also contained in the thiocyanate mixture. Patients were unaware of the change from one treatment phase to the next.

The electrocardiograms of the treated patients were studied as set out hereafter.

Of the thirty-six subjects in the control group all but nine were women. Ages ranged from 41 to 78 years, blood pressures from 180 to 260 mm. Hg systolic and from 100 to 150 mm. Hg diastolic. All patients were ambulatory. The treatment in this group consisted of the measures that make the traditional treatment of hypertension indistinguishable from that used in functional disorders: rest, mild sedatives, and reassurance, over periods ranging from 4 to 48 months.

RESULTS

In the fifty thiocyanate-treated patients, symptomatic improvement coincided with administration of the drug in forty. Remission seemed complete in twenty-eight, partial, in twelve patients. When thiocyanate was again replaced by the placebo, relapse occurred in only eleven patients, the return of symptoms being partial in six and complete in five. It would appear that in only eleven cases (22 per cent) are we justified in assuming a causal connection between thiocyanate treatment and symptomatic improvement.

TABLE I. BLOOD PRESSURE DROP DURING THIOCYANATE ADMINISTRATION, AND BLOOD PRESSURE RISE AFTER WITHDRAWAL OF THE DRUG, IN THE FIFTY HYPERTENSIVE PATIENTS

EXTENT OF FALL	10% OR OVER	15% OR OVER	20% OR OVER	FALL TO NORMAL	RISE TO INITIAL
Fall during thiocyanate period (No. of patients)	33 (66%)	10 (20%)	7 (14%)	2 (4%)	—
Rise during terminal placebo period (No. of patients)	17 (34%)	6 (12%)	2 (4%)	—	11 (22%)

In the group of eleven patients in whom symptomatic relapse followed thiocyanate withdrawal, the blood pressure rose in only two. Of the seventeen patients discussed below, in whom the blood pressure rose by 10 per cent or more after thiocyanate withdrawal, symptomatic relapse occurred in only two. This, and the fact that subjective improvement frequently preceded the apparent blood pressure drop, suggests that symptomatic improvement in these patients was independent of the behaviour of blood pressure.

During the thiocyanate period, of the fifty patients in the hypertensive series thirty-three showed a drop of 10 per cent or more of both the diastolic and systolic blood pressures (Table I). This includes ten patients with a fall of 15 per cent

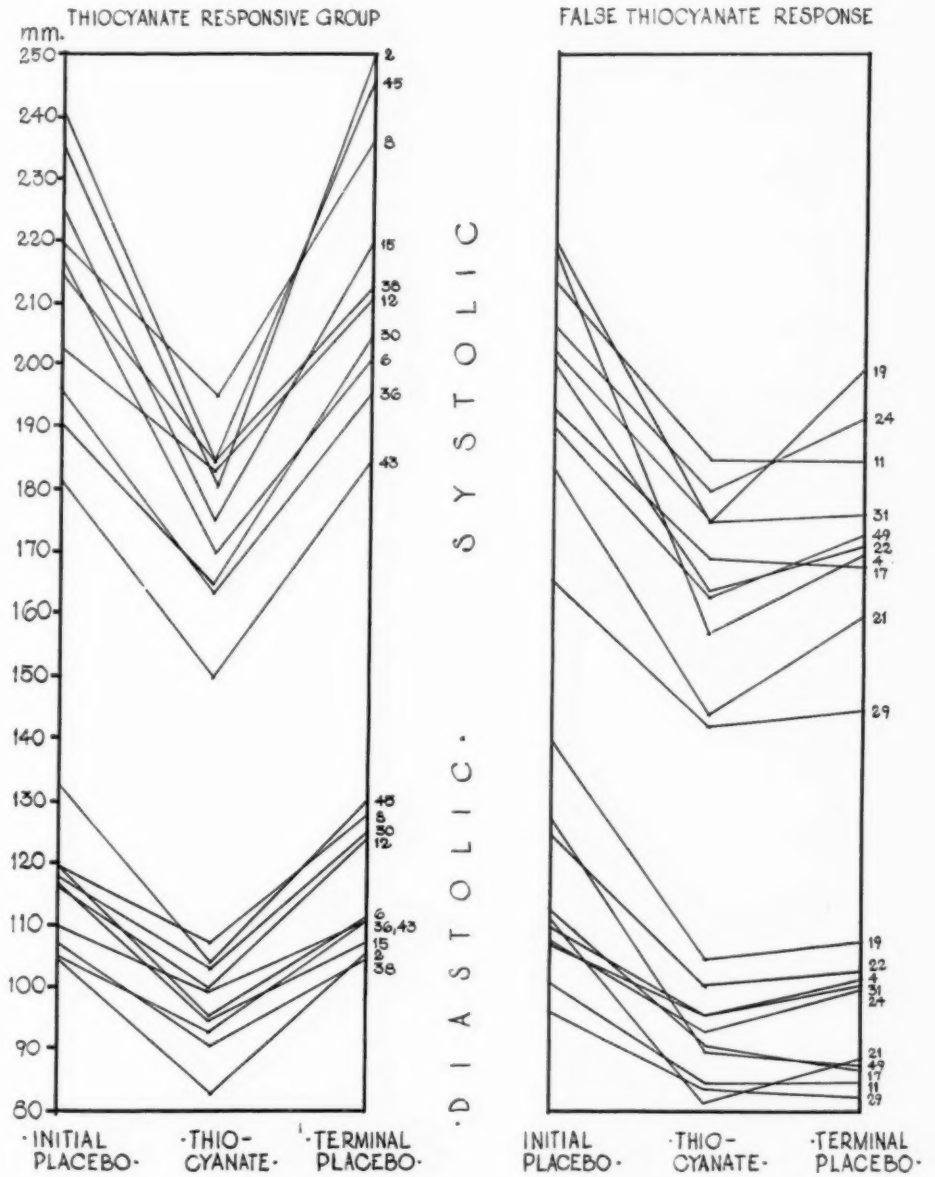

Fig. 1.—Blood pressure response to administration and subsequent withdrawal of thiocyanate in twenty representative cases. Left side: Ten subjects showing a rise of at least 10 per cent in both systolic and diastolic blood pressures after withdrawal. Right side: Ten patients where the fall accompanying administration of the drug was not followed by a similar systolic and diastolic increase on withdrawal.

or more, and seven patients with a fall of 20 per cent or more. In two the blood pressure returned to normal. During the terminal placebo period seventeen patients showed a blood pressure rise of 10 per cent or more. This includes six patients with a rise of 15 per cent or more, and two patients with a rise of 20 per cent or more. The blood pressure returned to the initial level in eleven subjects. In eleven subjects a rise of less than 10 per cent occurred, in five, no rise was obtained. (Fig. 1.)

In the control series of thirty-six nonthiocyanate-treated patients, twelve (33 per cent) showed a fall of 10 per cent or more of both the systolic and diastolic pressures (Fig. 2). This included four patients with a fall of 15 per cent or more.

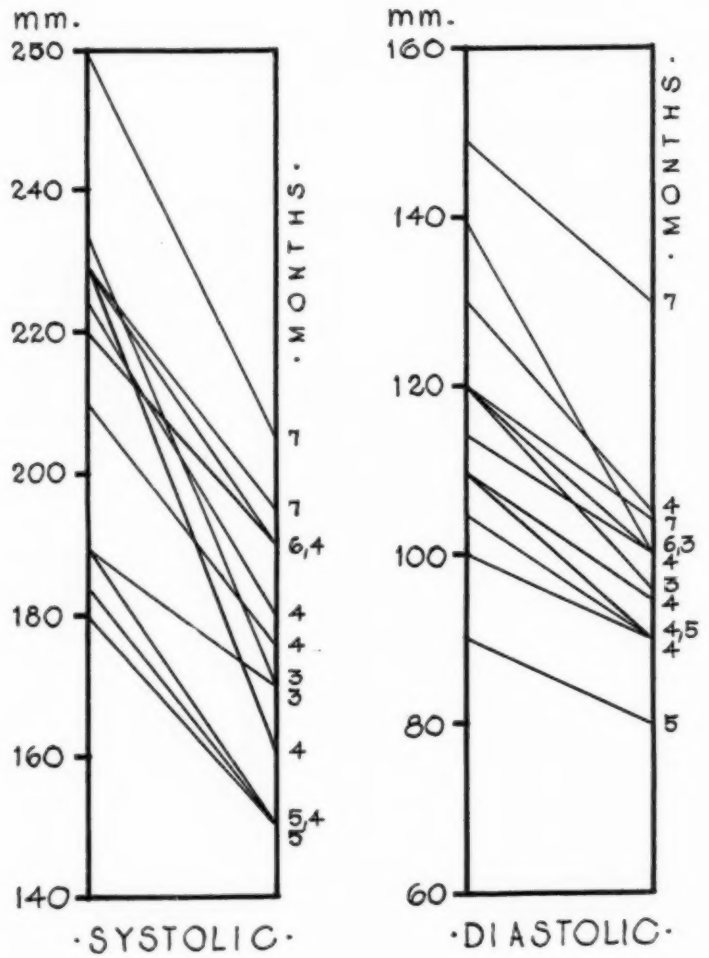

Fig. 2.—Twelve patients of the hypertensive control series of thirty-six, in whom a gradual fall of the systolic and diastolic pressures occurred without thiocyanate administration. The figures in the graph indicate the number of months required to reach the lowest level.

In two patients each of this group, the lowest blood pressure level was reached in the third, fifth, and seventh months of treatment, respectively. In five patients it occurred in the fourth, and in one in the sixth month.

Thus, during the thiocyanate period, 34 per cent of the treated group failed to show a blood pressure drop, in a further 32 per cent, a rise of less than 10 per cent or no rise occurred on thiocyanate withdrawal. In this group it may be assumed that most of the fall accompanying thiocyanate administration would have occurred had nothing but a placebo been given. This assumption is supported by the finding that in the control series 33 per cent of patients showed a fall without thiocyanate administration.

It has been demonstrated[9,10,11] that sympathectomy will frequently reverse abnormal changes in the hypertensive electrocardiogram. It therefore seems reasonable to demand such action in at least a proportion of patients, before attributing a depressor effect to any therapeutic measure. Although Barker[12] states that electrocardiographic improvement frequently occurs following the use of thiocyanate, a detailed study has not yet been published.

Of the fifty patients in the present hypertensive series, electrocardiograms were taken in forty-six. The three limb leads and Leads V_2, V_3, V_4, V_5, and V_6 were recorded in a total of 145 tracings, the number in a single patient varying from two to six.

White and his co-workers[11] found T_1 improvement in 47.1 per cent of hypertensive patients following sympathectomy. Of the forty-six thiocyanate-treated patients studied in the present series, only four have shown a favorable change of T_1 (elevation of 1 mm. or more). These changes were not reversed by thiocyanate withdrawal, nor did they coincide with a lowering of blood pressure. A shift of the electrical axis by 15 degrees or more, regarded as another criterion of improvement[11,13] was found after sympathectomy by the above authors in 29.8 per cent of patients. In the present series it occurred in only two patients; after 3 months of thiocyanate treatment in one and unrelated to treatment in another. No significant change was found in the chest leads.

DISCUSSION

In the present series the number of subjects showing symptomatic improvement and a blood pressure drop while receiving thiocyanate, was approximately twice as high as the number of those who relapsed after withdrawal of the drug. This suggests, that unless the improbable assumption of a spontaneous cure, or of thiocyanate effect outlasting the presence of measurable blood levels is made, in a number of patients the greater part of the drop in blood pressure is not due to the drug. It also shows that the effectiveness of a given treatment measure will be overestimated if judged by the blood pressure fall coinciding with its application.

A blood pressure reduction of 10 to 15 per cent[14,15] or of 20 to 40 mm. Hg diastolic and of 30 to 60 mm. Hg systolic[16,17] has in the past been regarded as a criterion of a favorable response to thiocyanate treatment. One must doubt the significance of such arbitrary standards, seeing that in a series of hypertensive

patients kept at rest for periods of 2 to 4 hours while blood pressures were repeatedly taken, the average systolic pressure fell by 44 mm. Hg (23 per cent), the diastolic by 18.5 mm. Hg (18 per cent).[18] This was ascribed to rest, and to habituation to the process of blood pressure measurement. One-third of the present nonthiocyanate-treated control group showed a gradual blood pressure drop of 10 to 20 per cent, illustrating that the factor of rest omitted, habituation to blood pressure measurement and the psychological effect of organized treatment are still able to produce a similar though less pronounced effect. The range of blood pressure reduction by such incidental factors widely overlap with the ranges of blood pressure reduction defined as significant in previous work.[14-17] If, on the other hand, a blood pressure fall in excess of that due to these factors were chosen to indicate drug effect, the observer would in most cases also miss a lesser fall produced by the drug. This renders definition of a 'significant' *fall* impracticable.

From the blood pressure rise following thiocyanate withdrawal a depressor effect of the drug may be inferred in a third of the subjects. The two controlled studies initially quoted,[7,8] and Alstad's[19] observations on thiocyanate effect on the basal blood pressure also suggest that the drug has some depressor effect. On the other hand it is not known how far a 10 to 25 per cent drop in blood pressure does actually move the patient towards the higher life expectation belonging to his after-treatment pressure,[20] since renal clearance,[21] skin temperature, the oscillometric arterial pulsations and carotid sinus sensitivity[8] and, as shown in the present series, the electrocardiogram, remain unaltered.

The suggestion that the substance was a natural depressor,[14] remained unconfirmed.[22,23,24]

SUMMARY

In over two-thirds of a series of patients with essential hypertension, thiocyanate administration was accompanied by a diastolic and systolic blood pressure fall of 10 to 25 per cent, and by symptomatic remission. Only one-third of the series showed a comparable rise after withdrawal of the drug. In a further one-fifth, a rise of less than 10 per cent occurred.

The causes of this discrepancy are discussed, as is also the significance of the blood pressure drop attributed to thiocyanate.

A spontaneous fall of blood pressure took place in one-third of patients in a nonthiocyanate-treated control series observed over some months.

The reversal of electrocardiographic abnormalities, known to occur in hypertensive patients after sympathectomy, was not observed after the administration of thiocyanate.

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COLD PRESSOR TEST FOLLOW-UP STUDY FOR SEVEN YEARS ON 166 OFFICERS

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EMPIRICAL evidence in regard to the validity of the cold pressor test as a criterion of the risk of developing hypertension is presented in this paper. The test was administered to 166 officers on active duty in 1940, some flying, some non-flying. Their annual blood pressures and physical examinations were followed through to 1947. In 1940 certain cumulative experience in the medical literature indicated that the cold pressor test could discriminate between normal individuals and prehypertensive individuals with normal blood pressures. When the testing was performed it was proposed that if these findings could be substantiated on flying officer personnel, the cold pressor test could be added to the collection of selection and classification techniques of aviation medicine.

The literature before 1940 begins in 1932 when Hines and Brown[1] standardized and popularized the cold pressor test. According to conventions arbitrarily established by these workers,[1,2,3,4] individuals with an index (maximum blood pressure rise) of 20 or less are called "hyporeactors," and individuals with an index of 21 or more are called "hyperreactors." Hines and Brown observed extreme hyperreaction in patients with hypertension (indices often exceeding 40) and conjectured that there is a tendency for hyperreactors to become hypertensives if they are not so already. Hines[5] examined family histories of subjects for hereditary predisposition toward hypertension, and found a higher rate of predisposition among hyperreactors than among hyporeactors. He also followed for three years a small number of hyporeactors who developed hypertension. Meanwhile related studies were reported in the literature by Yates and Wood,[6] Briggs and Oerting[7] and others. Ayman and Goldshine,[8] in 1938, critically reviewed the literature on the cold pressor test and reported further measurements on hypertension and normal subjects. Only a small number of hyperreactors were tested, and no hereditary nor follow-up studies were conducted. Up to this point the frequency of hyperreactors in the general population of adults with normal blood pressure (systolic 140 mm. Hg or less, diastolic 90 mm. Hg or less) had been quite well established at about 25 per cent, and the average systolic-diastolic index at about 12 to 10 per cent for hyporeactors and at 35 to 25 per cent for hyperreactors. Again, in 1940, Hines[4] reviewed his conclusions that "this type of vascular hyperreactivity represents a 'pre-hypertensive' phase of the syndrome which is designated as essential hypertension," and summarized his experience

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of several thousand measurements. New qualitative evidence for these contentions was presented. A six-year follow-up on about three-fourths of an earlier group of sixty-six normal subjects showed the development of hypertension in about one-third of the hyperreactors and in none of the hyporeactors.

Subsequent investigators had difficulty in reproducing many of the findings of Hines and Brown. In 1942, Feldt and Wenstrand[9] found no difference in family histories between hyporeactors and hyperreactors in 359 subjects. In 1943, Russek[10] also found no relation between reaction and family history in 200 subjects and reported a trend in index with age. In 1944, Todd[11] found no relation between family history and reaction in 88 university students, and found poor reproducibility of repeated measurements on the same individual. In 1945, Russek and Zohman[12] reported further evidence of a correlation between cold pressor index and age. Bruce, Martin, and Smirk[13] found no relation between initial blood pressure level and cold pressor index. Finally, the seven-year follow-up study on 166 officers reported herein fails to corroborate the belief that the cold pressor test index is valuable as a predictor of the tendency to develop high blood pressure in a selected group of the population.

TECHNIQUE

In January, 1940 the cold pressor test was administered to 186 flying and non-flying officers at Wright Field as follows: the subject reclined for five minutes or longer, until his blood pressure stabilized. His right hand was immersed in ice water at 4° C. for one minute and then removed. Blood pressure on his left arm was taken thirty seconds and sixty seconds after the hand was immersed and again sixty seconds after it was removed. The cold pressor test *index* was defined as the difference between the resting systolic blood pressure and the highest systolic blood pressure subsequently recorded during the test.

The name, army serial number, and other identifying information were recorded on each subject. In 1947, this information was used by a team of follow-up study clerks who located the medical files of 166 of the original 186 officers in the Adjutant General's records depots in Washington, D. C., and St. Louis, Mo. The annual physical examination blood pressures were transcribed for each subject. All medical records on each subject, sick calls, hospitalizations, proceedings of retirement boards, etc., were examined for evidence of cardiovascular disease during the follow-up period. Pertinent clinical remarks and data were abstracted.

RESULTS

The age, resting blood pressure, cold pressor test, and flying time constitute the relevant test variables recorded in 1940. The annual blood pressures from 1941 through 1947 and the cardiovascular history constitute the relevant follow-up variables. All told, these relevant variables number more than thirty, considering all diastolic and systolic measurements. In order to reduce the variables

TABLE I.

STATISTICAL SUMMARY OF THE COLD PRESSOR TEST INDEX, MEASURES OF HYPERTENSIVE TENDENCY, AND OTHER VARIABLES IN THE SEVEN-YEAR FOLLOW-UP STUDY OF 166 OFFICERS. (ONE-BY-ONE THROUGH NINE-BY-NINE MATRIX ENTRIES ARE CORRELATION COEFFICIENTS).

VARIABLE → / ↓	1 AGE	2 INDEX (COLD PRESSOR)	3 FLYING TIME	4 BASAL SYSTOLIC	5 BASAL DIASTOLIC	6 SYSTOLIC RISE	7 DIASTOLIC RISE	8 SYSTOLIC INCREMENT	9 DIASTOLIC INCREMENT
1 AGE		−.04	.42†	.21*	.45†	.29†	−.17	.32†	−.02
2 INDEX (COLD PRESSOR)	−.04		−.06	.10	.02	−.07	.04	.10	−.09
3 FLYING TIME	.42†	−.06		.08	.28†	−.04	−.17	.09	−.11
4 BASAL SYSTOLIC	.21*	.10	.08		.67†	−.09	−.17	.20*	−.05
5 BASAL DIASTOLIC	.45†	−.02	.28†	.67†		.06	−.52†	.29†	−.32†
6 SYSTOLIC RISE	.29†	−.07	−.04	−.09	.06		.38†	.55†	.33†
7 DIASTOLIC RISE	−.17	.04	−.17	−.17	−.52†	.38†		.09	.69†
8 SYSTOLIC INCREMENT	.32†	.10	.09	.20*	.29†	.55†	.09		.46†
9 DIASTOLIC INCREMENT	−.02	−.09	−.11	−.05	−.32†	.33†	.69†	.46†	
Means	36.5 (YEARS)	10.1 (MM. HG)	27.4 (MONTHS)	110.5 (MM. HG)	73.0 (MM. HG)	16.8 (MM. HG)	8.9 (MM. HG)	1.77 (MM. HG)	.5 (MM. HG)
Standard Deviations	7.9	5.7	15.0	11.1	8.7	10.1	8.6	3.1	1.8
Ranges	22 to 56	0 to 30	2 to 69	94 to 170	58 to 115	−4 to 34	−16 to 32	−2.5 to 26.0	−5.0 to 12.0

*Significant at .05 level in the test of the null hypothesis of no correlation.
†Significant at .01 level.

for analysis to a comprehensible and manipulatable number, the following definitions were made:

x_1 = Age of subject in 1940.

x_2 = Systolic index of the cold pressor test in 1940.

x_3 = Cumulative flying time as of 1940 recorded in hundreds of hours.

x_4 = Basal (resting supine) systolic pressure before the cold pressor test in 1940.

x_5 = Basal diastolic pressure. (Analogue of x_4).

x_6 = Systolic rise from 1940 to 1947. The difference between x_4 and the highest subsequent blood pressure recording during the follow-up years.

x_7 = Diastolic rise from 1940 to 1947. (Analogue of x_6).

x_8 = Systolic increment per year from 1940 to 1947.*

x_9 = Diastolic increment per year from 1940 to 1947. (Analogue of x_8).

x_{10} = Follow-up status. x_{10} takes on the code values: (1) on active duty throughout follow-up period, 104 subjects; (2) left follow-up study during 1940-1947 for noncardiovascular reasons, 42 subjects; (3) relieved from active duty during 1940-1947 for cardiovascular disease but not hypertension, 17 subjects; (4) developed hypertension during follow-up period, 3 subjects.

Variables x_1 through x_5 are the clinical measurements on which prognosis is to be based, provided they are found to be effective predictors. Variables x_6 through x_9 are quantitative measures of high blood pressure tendencies during the follow-up period. In brief, then, the object of this investigation is to find the correlation between the set $x_1 - x_5$ and the set $x_6 - x_9$, with particular reference to the intercorrelations with x_2, the cold pressor test index.

Statistical computations on all 166 subjects are summarized conveniently in Table I, which contains the complete correlation matrix of the nine quantitative variables (x_1 through x_9) and the mean, standard deviation, and range of each of these nine variables. The entries in Table I are conventional product-moment correlation coefficients,[11] which denote perfect correlation with values ± 1, degrees of correlation with values between ± 1, and no correlation with value zero. Correlation coefficients are subject to sampling variations from sample to sample depending on the sample size. In Table I coefficients believed to be non-zero, thus denoting some correlation, are labelled with asterisks or daggers.

Thirty-six of the subjects in this study are non-flying personnel. Although separate statistical computations were performed on this group, the results were so similar that the composite results only are shown in Table I. However, precaution should be exercised in interpreting correlations with flying time (x_3). Such correlations apply only to career flyers who accumulate flying time monthly.

STATISTICAL AND CLINICAL INTERPRETATIONS

A recapitulation of the salient results listed in Table I will facilitate discussion. First, cold pressor test index in this study is found uncorrelated with

*$x_8 = b' = (\Sigma yt - N\bar{y}\bar{t})/(\Sigma t^2 - N\bar{t}^2)$, the least squares estimate of b the slope of the line $y = a + bt$, where y is the systolic blood pressure for the year t.

measures of the tendency toward high blood pressure. Second, the basal diastolic and systolic blood pressure of an individual, as well as his tendency to increase in systolic pressure in later life, are correlated positively* with age. Third, basal diastolic pressure is correlated with the measures of tendency toward high blood pressure (some positively, some negatively). Fourth, flying time is uncorrelated with measures of the tendency toward high blood pressure. Fifth, the four measures of tendency toward high blood pressure (x_6, x_7, x_8, x_9) are generally positively correlated, as expected from their closely allied definitions.

A synthesis of the foregoing statements and a detailed scrutiny of Table I lead one to the conclusion that *in predicting blood pressure increase in later life, age and basal diastolic pressure are relevant, whereas cold pressor index and flying time are irrelevant.* Several authors were cited in the introductory paragraphs who gave credence to the prognostic value of the cold pressor test. It could be argued that the present study contains few hyperreactors, subjects expected to develop hypertension, and therefore that this study does not constitute a valid trial of the prognostic value of the cold pressor test index.† A rebuttal based on the arbitrariness of the definition of "hyperreactor" is available. Early investigators chose an index of 22 as the boundary between hypo- and hyperreactors.[1-8] Later they chose 20.[4] Under the assumption that there is just one large population of normal blood pressures, the multi-correlational analysis of this paper is valid. Under the assumption that hyporeactors and hyperreactors are distinct populations, the analysis of this paper is not completely valid; but neither is arbitrariness in establishing the point of demarkation. Needed is a mathematical model of the population supported by data.‡

That flying time is found irrelevant to hypertensive tendencies is rather surprising. One might presume that the physical and psychological stresses of flying would cumulate within an individual and be reflected in "a general deterioration of the cardiovascular system"[16] manifested in some subjects by hypertension. It could be that the annual physical examinations on the flyers over a period of years somehow continuously screened potential hypertensives so that few were actually included in the sample of officers tested in this study.§

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*Positive correlation means that two variables tend in the same direction. For instance, the older a person is relative to the mean age of persons in a group, the higher is his annual increase in systolic blood pressure relative to the mean annual increase.

†Among the 166 officers in this study, three developed hypertension. Their indices were 12, 4, and 14. Six officers in this study were hyperreactors. Their indices were 28, 22, 22, 30, 22, 30. Only the fifth developed cardiovascular disease (generalized arteriosclerosis); none showed excessive rise or increment of pressure in the follow-up period.

‡On a priori grounds, the cold pressor test index may have merit as an indicator of the vasomotor stability of an individual at the time of measurement. The inability of the index to develop significant correlation with age, initial blood pressure, and measures of hypertensive trends may be due to poor reproductibility of data on the same individual, or low "reliability" in statistical terms.[15]

§Such a serial screening procedure, if founded in clinical estimations of vasomotor stability, say, with the Schneider Index or with the variability of blood pressure readings, would tend to result in the selection of officers with low cold pressor test indices. This screening may account for the small number, six, of hyperreactors among these 166 subjects, otherwise selected at random, whereas about one-fourth of persons are expected to be hyperreactors. It does not, however, seriously affect the multicorrelation analysis,[17] because the amount of truncation of the population is not large.

That age is related to hypertensive tendency is not an uncommon belief. At least it is often said that as one grows older he can expect a gradual rise in his basal systolic and diastolic pressures. The correlation coefficients of .29 and .32 of age with systolic rise and increment, respectively (entries in cells 1,6 and 1,8 or 6,1 and 8,1) in Table I suggest moreover that the rate of increase of systolic pressure increases with age. This in turn implies a curvilinear regression of systolic pressure on age, a conclusion in agreement with the large-scale statistical studies of Robinson and Brucer.[18]

Certain reservations should be made. The magnitude of the correlation coefficients in Table I should not be taken too seriously. That they are or are not evidence of relationship between the variables is important. In considering prognostic value, none of them possesses high predictive efficiency. In a way, this study may be called a 'preliminary report' based on the experience of a seven-year follow-up. Perhaps in ten or twenty more years a 'final report' on these same subjects, with new data and a re-examination of the statements made here, should be prepared. Moreover, it should be emphasized that the data of this investigation were observed on a highly restricted part of the general population, as candidates for pilot training were carefully selected. During their careers, the subjects of this study had to maintain high physical standards to remain on flying status. Thus, the statistical phenomenon of the reduction of the correlation coefficient computed on a part of the population must be considered when the results are generalized to the whole population. These negative findings do not constitute conclusive disproof of the cold pressor test in general application.

SUMMARY

1. A seven-year follow-up study of annual blood pressures and cardiovascular histories of 166 officers is analyzed statistically in regard to cold pressor tests administered to them in 1940.

2. Cold pressor test index is found not correlated with measures of hypertensive tendency, with age, with flying time, or with basal blood pressure.

3. Basal diastolic and systolic pressure, and the tendency to increase in systolic pressure in later life, are found correlated with age.

4. Basal diastolic pressure is found relevant to trends in diastolic and systolic pressure in later life.

5. The number of hours a career pilot has flown is found not correlated with hypertensive tendencies, provided he has passed careful physical examinations annually.

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THE DIGITAL BLOOD PRESSURE DETERMINATION. III. A STUDY OF THE EFFECTS OF TETRAETHYLAMMONIUM CHLORIDE ON CARDIOVASCULAR DYNAMICS, MAKING USE OF BLOOD PRESSURE RESPONSES AT THE DIGITAL LEVEL

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THE blockade effect of the tetraethylammonium ion (TEA) on the autonomic ganglia was studied carefully during the early part of this century,[1] yet it has been only in the past few years that clinical use of this important blockade action has been considered. In this short period, however, it has been used extensively both as a therapeutic and diagnostic agent in diseases relieved by removal of autonomic tone.

TEA has been used to evaluate the vasospastic element of arterial insufficiency. Following its administration the rise in temperature produced in the involved extremity is observed. Failure to obtain this rise has suggested the presence of organic occlusive arterial changes.[2,3] The drug has also been used in an attempt to determine the neurogenic component of arterial hypertension as an aid in the selection of candidates for treatment by splanchnic nerve resection.[4]

A very wide range of changes in blood flow and blood pressure have been recorded in response to the administration of TEA to patients with these diseases and to normal subjects.[2-6] Little direct information is available regarding the factors responsible for this marked variability. We considered it pertinent therefore to study a group of twenty normal subjects in order to determine the range of the TEA effect unaltered by pathological factors. This study included the determinations of blood pressures at the levels of both the brachial and digital arteries, pulse rate, digital temperature, and electrocardiograms. The results proved informative not only as a basis for the interpretation of responses observed in patients with various diseases, but also yielded information about factors responsible for the wide variability in results observed.

MATERIALS AND METHODS

Of the twenty normal subjects who received TEA, sixteen were members of the University of California Hospital resident staff, and the remaining four were hospital patients with no evidence of cardiovascular disease. A control

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observation period of at least one hour was used in each case before the drug was administered. During this time the subjects remained recumbent, covered only by a light hospital gown. The room temperature was always between 20° C. and 24° C. and never varied over 1.5° C. during the course of any of the experiments. The observation period was continued for at least one hour after the intravenous administration of 300 to 500 mg. of tetraethylammonium chloride.* The drug was administered at the rate of 100 mg. per 20 seconds. Observations included brachial systolic and diastolic pressures, pulse rate, digital systolic pressure, electrocardiograms and skin temperatures over the following points: finger, wrist, deltoid, toe, ankle, and thigh. Digital systolic blood pressures were determined by placing a miniature pressure cuff about the proximal phalanx and blanching the distal part of the finger.[7] The pressure in the cuff was then raised above the systolic pressure and lowered gradually. The reading of digital systolic blood pressure was taken when the first spurt of blood was seen in the skin distal to the cuff. Skin temperatures were measured galvanometrically using copper constantan thermocouples fastened to the skin with adhesive tape.

RESULTS

Subjective Response.—Subjectively, the responses to TEA were similar to those previously reported. These included a metallic taste, numbness and tingling about the mouth and extremities, blurring of vision and dryness of the mouth, all lasting about 15 to 30 minutes. In addition, five of the normal subjects developed a definite generalized shaking about 10 minutes after the drug was administered. This activity seemed to be widespread muscular fibrillary twitching or fasciculation and only slight chilly sensation was experienced. The reaction lasted from 15 to 30 minutes. Two subjects with histories of respiratory allergy developed definite nasal congestion and complained of difficult breathing. This effect lasted throughout the second 15 minute period after the drug was administered.

Blood Pressure and Pulse Rate.—Figure 1 is presented to illustrate the marked variability of the changes in blood pressure produced by TEA in normal subjects. In Subject 10, TEA produced an initial fall in brachial systolic and diastolic pressures and also a fall in digital systolic pressure (Fig. 1,*A*); conversely, in Subject 4, the initial effect of the drug was to produce a rise in all three of these pressures (Fig. 1,*B*); while in Subject 6, TEA produced the paradoxical early changes of a rise in the brachial pressures while the digital pressure fell (Fig. 1,*C*). In all three it will be noted that regardless of whether the initial effect was a rise or a fall, there was a tendency for both brachial and digital pressures to rise and remain above the baseline values 15 minutes after the drug was administered. The pulse rate increased immediately in all three but to a different degree in each.

In Fig. 2, a summary of the maximum immediate changes and of the late effects produced by the drug on blood pressures and pulse rate is presented. Values indicated as "late effects" represent the mean variation from the baseline readings observed between 15 minutes and one hour after TEA administration. A change in blood pressure of over 5 mm. Hg was considered significant.

*Etamon, made available for this work through the courtesy of Parke, Davis and Company.

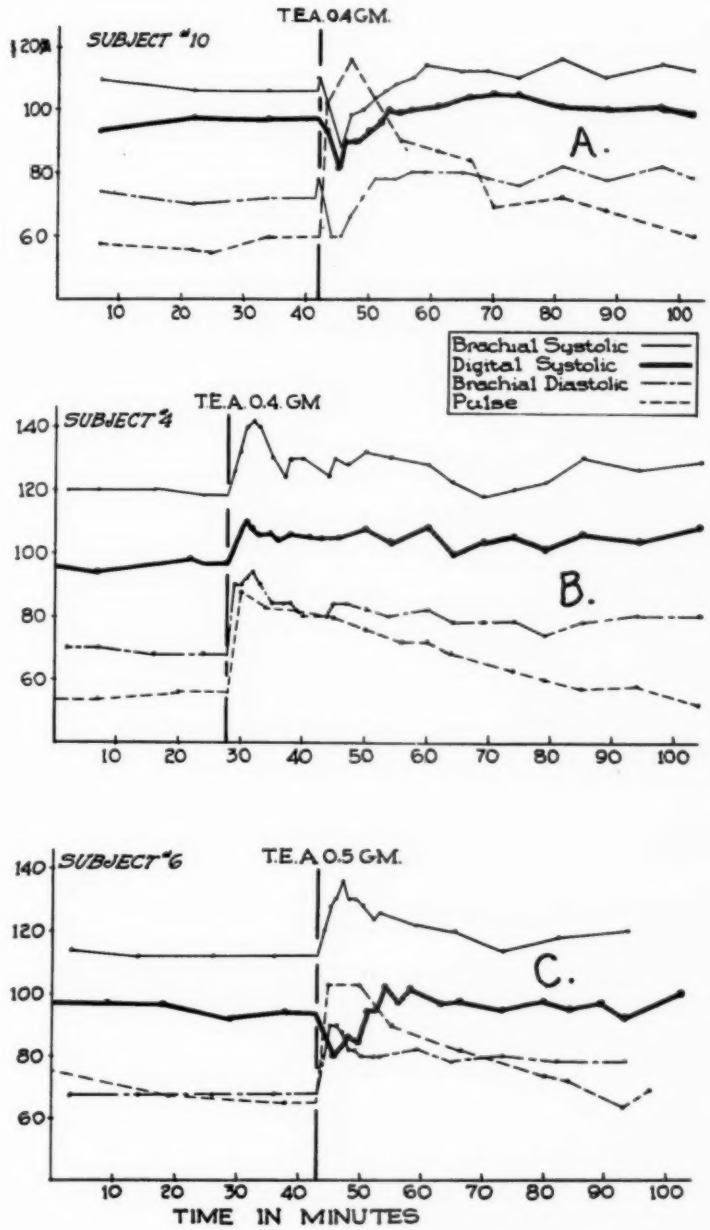
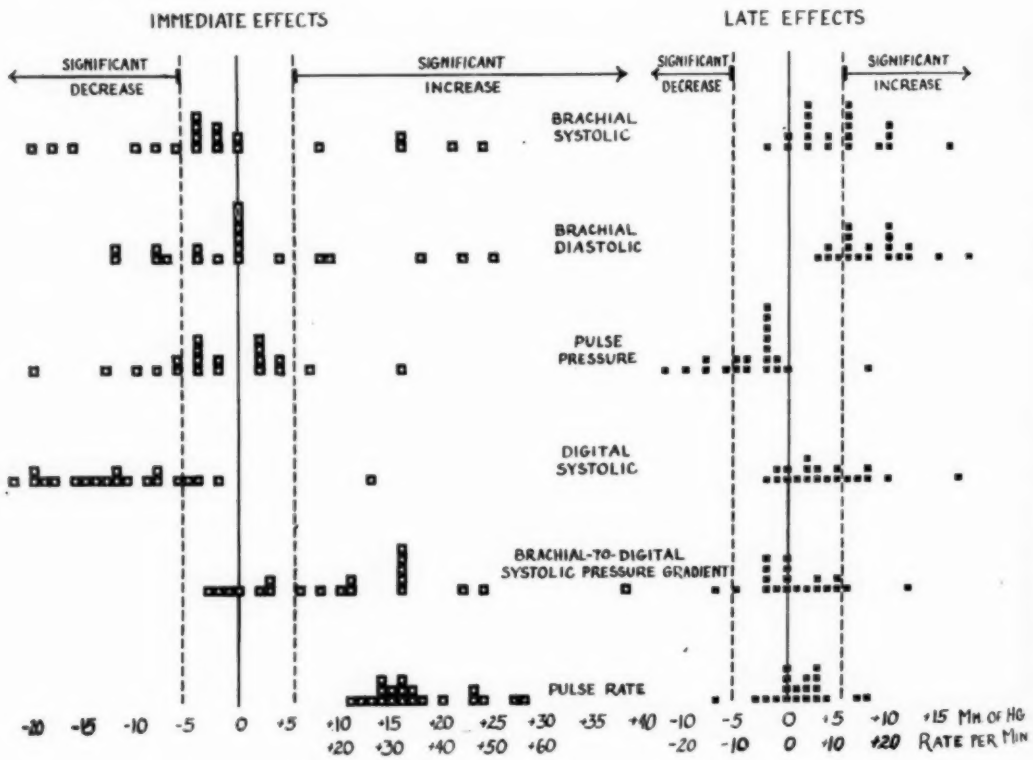


Fig. 1.—Changes in blood pressure in response to TEA administration in three normal subjects' Ordinates represent blood pressure or pulse rate while the abscissa are taken in minutes. Graph "A" shows a fall in both brachial and digital pressures while in "B" the pressure at these two levels of the arterial tree rose. Graph "C" demonstrates the paradoxical effect of a fall in digital pressure while the brachial pressure rises.

A consideration of the immediate effects indicates that although a wide scatter in the magnitude and direction of the changes in blood pressure is apparent, certain trends in these changes are evident. While these normal subjects responded to the administration of TEA with either a significant rise or fall, or no change at all in brachial systolic, diastolic, and pulse pressure, the digital systolic pressure fell significantly in 16 of the 20 subjects. The tendency to obtain a greater fall in pressure at the level of the digital artery than at the brachial level is reflected in the distinct increase in the pressure gradient between these two levels.


IMMEDIATE EFFECTS
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BRACHIAL SYSTOLIC
BRACHIAL DIASTOLIC
PULSE PRESSURE
DIGITAL SYSTOLIC
BRACHIAL-TO-DIGITAL SYSTOLIC PRESSURE GRADIENT
PULSE RATE
-20 -15 -10 -5 0 +5 +10 +15 +20 +25 +30 +35 +40 -10 -5 0 +5 +10 +15 MM. OF HG
+20 +30 +40 +50 +60 -20 -10 0 +10 +20 RATE PER MIN

Fig. 2.—A summary of the immediate effects (large hollow squares) and late effect (small solid squares) of TEA on the blood pressure and pulse rate of twenty normal subjects.

In contrast to the variable immediate effects of TEA on the brachial systolic, and diastolic pressure, these pressures were consistently above the basal level about 15 minutes after the drug was administered. This rise was also seen in the digital systolic pressure, but to a lesser degree. In all three pressures the rise, though consistent, was not great; frequently being too small to be considered significant. This rise occurred whether the initial effect of the drug was to produce a rise or a fall in pressure. None of these pressures was significantly below the basal level 15 minutes following injection. The pulse pressure on the contrary decreased slightly but consistently, reflecting a greater rise in brachial

diastolic than systolic pressure. In the period designated "late effects" the brachial-to-digital pressure gradients were essentially unaltered from their baseline values.

In summary, while the immediate effects of TEA on blood pressure at the level of the brachial artery were variable, there was a consistent fall in blood pressure in the smaller arteries of digital size, resulting in a significant increase in the brachial-to-digital pressure gradient. The late response to the drug was a definite but slight elevation in blood pressures at both brachial and digital levels regardless of whether the initial effect was a rise or a fall.

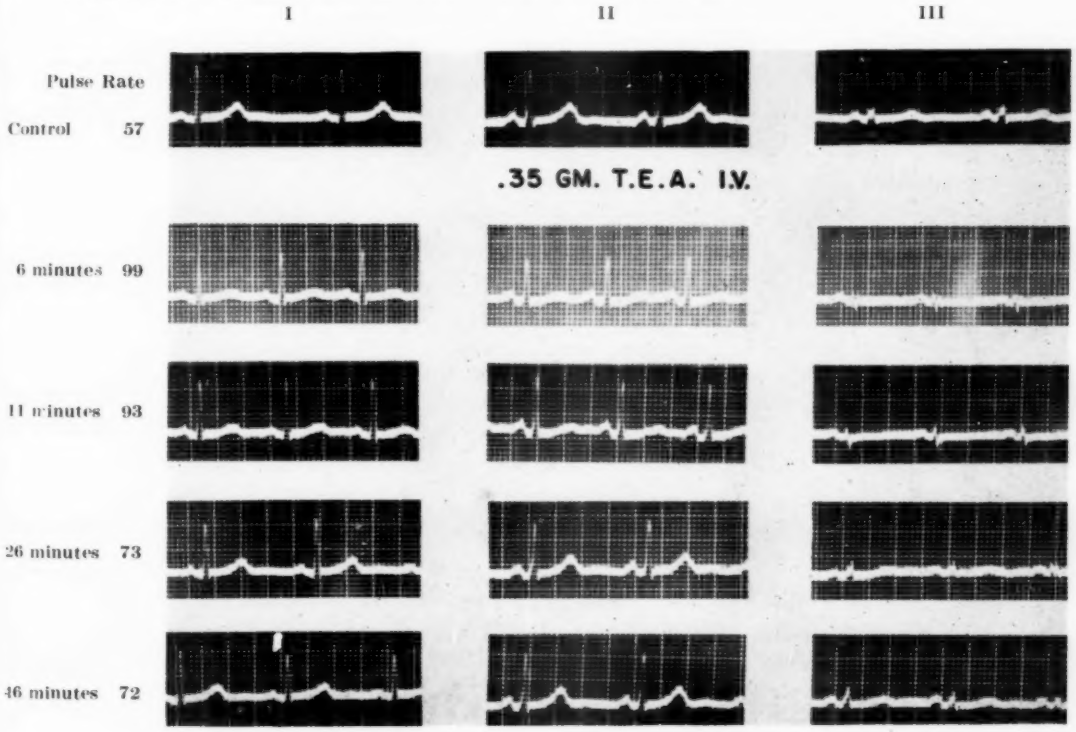


Fig. 3.—Standard lead electrocardiograms taken before and at intervals after administration of TEA to a normal subject.

Tetraethylammonium invariably produced an immediate rise in pulse rate which varied from 26 to 113 per cent above the basal level. In most subjects, the heart rate had returned to normal one hour after the administration of the drug.

Electrocardiographic changes were variable and never striking. In the majority of these normal subjects there was an inversion or a lowering of the T wave most marked in Lead III and lasting 15 to 30 minutes (Fig. 3).

Skin Temperature.—In order to use TEA diagnostically in evaluating the part played by occlusive changes in arterial insufficiency, it is essential to know the extent and variability of the temperature rise that will be produced by the

drug in the extremities of normal subjects. If it can be demonstrated that normal digits at a certain temperature will respond to the drug by a specific quantitative rise in temperature, patients whose digital temperature rises less than this amount may be assumed to have some occlusive arterial change. Unfortunately, even in the normal subjects no such consistent rise in temperature was observed. In Fig. 4, the rise in temperature of the digits in response to the administration of TEA is plotted against the digital temperature at the end of the control period. Considering that 32° represents the temperature of a completely dilated

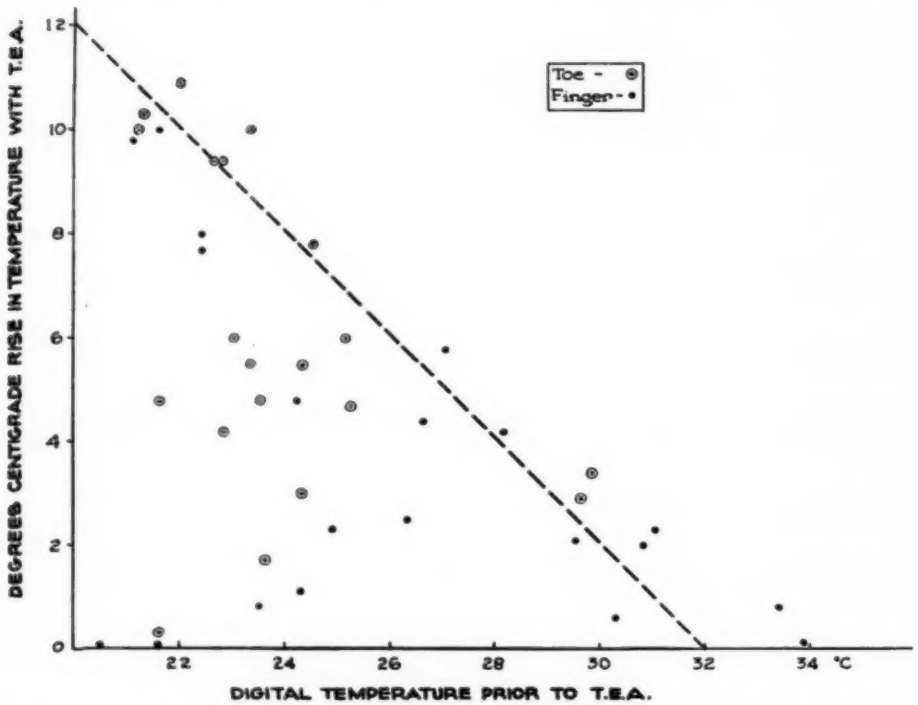


Fig. 4.—Changes in finger and toe temperatures following the administration of TEA to twenty normal subjects.

digit, all points representing maximal dilatation should reach the line connecting 32° on the abscissa with 12° on the ordinate. Finger and toe temperatures that were around 24° C. at the beginning rose anywhere from 1° C. to 10° C. when TEA was administered. Toe temperatures rose consistently more than finger temperatures and remained elevated longer.

DISCUSSION

The finding of a marked variability in the effect of TEA on the blood pressure and blood flow in both normal and abnormal subjects has been noted by numerous investigators.[1-6] The clearcut demonstration of this variability in our current work warrants a re-evaluation of the factors probably responsible for this lack of uniformity of response. Four factors which we consider to be

of special importance are: 1) variations in basal autonomic tone; 2) completeness of blockade of autonomic ganglia; 3) various sites of action, and 4) abnormal conditions.

1) *Variation in Basal Autonomic Tone.*—The major pharmacologic action of TEA has been adequately demonstrated to be a blockade of autonomic nerve transmission at the level of the sympathetic and parasympathetic ganglia. If no autonomic impulses are being transmitted to the effector organ, no change would be anticipated when the drug is given. This fact has been demonstrated by the failure of TEA to produce a change in cutaneous blood flow in a sympathectomized extremity[3,8] and by absence of an effect on blood pressure when the drug was administered to a cat after the spinal cord had been severed just below the medulla.[9] Similarly, if the vascular supply to the hand has been completely dilated by heat the sympathetic vasoconstrictor tone to the hand will be absent and administration of TEA cannot further lower this autonomic activity which is already zero. Conversely, however, if the autonomic vasoconstrictor tone to the extremity is high, its interruption by TEA blockade would be expected to produce a great change in blood flow.

It is reasonable to assume that if the TEA blockade of the ganglia were complete, the extent of the change produced by the drug would be directly proportional to the amount of autonomic activity that had been relayed over the ganglia before it was blocked. On this basis, Moe and his associates[10] have used the magnitude of the blood pressure response to TEA as a means of evaluating the amount of vasomotor activity in dogs after carrying out various procedures designed to alter cardiovascular balance. Following hemorrhage the effect of the drug was increased, indicating increased vasomotor activity; while after administration of epinephrine, the effect of the drug was diminished suggesting that epinephrine produced a decrease in vasomotor tone.

The principle that the differences in basal autonomic tone are responsible for the variable effects of TEA serves as a basis for the use of this drug in the evaluation of patients with hypertension for sympathectomy.[4] If a marked fall in blood pressure is obtained with TEA, it is assumed that the sympathetic tone is high and that sympathectomy might also produce this desirable result. Failure to obtain a fall in blood pressure is said to suggest a low degree of sympathetic vascular tone.

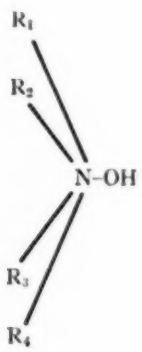
Thus one factor that must be responsible for variations in blood pressure and blood flow changes in response to TEA is the difference in basal autonomic tone in different individuals. It is also probable that variations exist in the basal autonomic tone in different branches of the vegetative nervous system controlling the cardiovascular dynamics of a given individual.

2) *Completeness of Blockade of Autonomic Ganglia.*—It is obvious that uniform changes in blood pressure and blood flow may be anticipated in response to TEA only if it is given in amounts which will produce a complete blockade of autonomic ganglia, or if the degree of blockage is uniform. There seems to be ample evidence that this is not the case when TEA is employed in the dosage used in man.[3,5,6] Of our twenty subjects who had no evidence of organic vascular

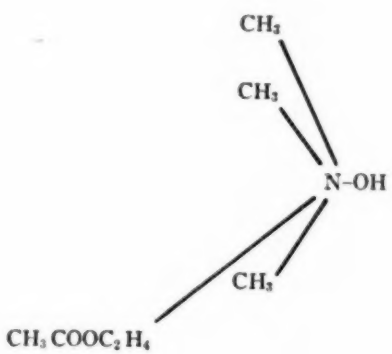
obstruction, only ten showed evidence of maximally increased blood flow in both the upper and lower extremities with the administration of 300 to 500 mg. of tetraethylammonium. The effect of the drug on cutaneous blood flow varied from a minimal detectable change to apparently complete vasodilatation. While this variability in skin temperature changes is evidence of difference in individual susceptibility to blockade by TEA, evidence of regional differences in susceptibility in a given individual was established by the finding that the response was consistently greater in the lower extremities than in the upper. This finding has been recorded by others.[3]

This evidence suggests that TEA in the dosage used did not produce a uniform blockade to the transmission of vasomotor impulses through all the sympathetic ganglia supplying the skin of the extremities. Furthermore, there is no reason to suppose that the drug produces a constant degree of blockade of the vasomotor impulses to other vascular beds in all individuals. Variable degrees of sympathetic blockade in the visceral vascular bed may well be responsible for some of the marked variations seen in blood pressure response to tetraethylammonium.

It appeared evident in our series of normal subjects that in those persons with clinical evidence of higher vasomotor activity as shown by their rapid cooling, the drug was less effective in producing a blockade of the autonomic ganglia than in the subjects who cooled slowly. In this connection it is pertinent to examine in more detail the probable mode of action of TEA in blocking the autonomic ganglia. Acheson and Pereira[11] have demonstrated that an autonomic ganglion blocked by TEA may still be stimulated by potassium chloride, but that it can no longer be excited by acetylcholine. Thus it is suggested that TEA interferes with the synaptic transmission of nerve impulses. Boyd and his associates[5] have pointed out the striking similarity in chemical structure of TEA and acetylcholine:



Quaternary Ammonium



Acetylcholine

Lyons and his associates[4] state that the blocking action of TEA depends on its ability to compete temporarily with acetylcholine at the synapse. It is our opinion that this action falls logically into the category of competitive inhibitions which has recently been recognized as a mode of action of a wide variety of pharmacologically active materials.[12] The competitive inhibition of acetylcholine by TEA at the synapse will depend not only on the concentration of TEA, but also on the amount of acetylcholine present. Where acetylcholine is present in excessive amounts, as might be expected in conditions of high autonomic tone, it may be anticipated that ordinary amounts of TEA may not be effective in competitively inhibiting the action of acetylcholine.

The validity of this principle is supported by the effect of the drug on a 43-year old patient with Raynaud's disease who had had a bilateral lumbar sympathectomy for hypertension in 1934. When examined in 1947 the left foot was much colder than the right and the patient was having frequent episodes of blanching and cyanosis of the hands. The increased vasomotor activity to the left foot was also demonstrated by the fact that this foot cooled more rapidly than the right on exposure to room temperature of 26° C. Figure 5 shows the effects of administration of 400 mg. of tetraethylammonium. The rise in temperature of the right great toe was rapid and maintained for over two hours. Temperature elevation of the left great toe was slightly delayed and much more brief. Temperature changes in the left hand indicated that there was no more than a suggestion of an increase in blood flow. The relative effectiveness of TEA in producing an increase in cutaneous blood flow in these three extremities was inversely proportional to the amount of vascular tone clinically evident. All three extremities had been observed on occasions to be capable of complete vasodilatation. Hence it seemed evident that the effectiveness of TEA in producing an autonomic ganglion blockade in this patient was inversely proportional to the number of impulses traversing the ganglion. In terms of our hypothesis, TEA in the dose used was capable of competitively inhibiting the action of acetylcholine only when the latter was present in small amounts.

There is no reason to suppose that there is less variability in the effectiveness of the TEA blockade of autonomic ganglia controlling vasomotor impulses to the viscera. Hence the inconsistencies of the responses observed in blood pressure may be based, to some extent at least, on the variable effect on the visceral vasomotor activity. On this basis, it is possible that the blockade will be less effective and the changes in blood pressure less marked where the autonomic activity or neurogenic element of hypertension is great.

3) *Various Sites of Action.*—Discussions of the mode of action of TEA by which changes in blood pressure and blood flow are produced have emphasized almost exclusively the dilatation it produces by autonomic ganglion blockade.[4,6,13] It would be well to consider other changes that the drug is capable of effecting which may also alter blood flow and blood pressure.

Acheson and Moe[9] by intra-arterial administration of TEA to dogs demonstrated that in high concentrations the drug would produce a pressor effect in the perfused limb. Using cats, these authors showed that while the effect of the drug in small doses was to produce a fall in blood pressure, doses of approx-

imately 10 mg. or more per kilogram caused a pressor effect. The mechanism responsible for this secondary pressor effect was not evident, but obviously it could not have been the result of vasodilatation. Reiser and Ferris[6] have pointed out that TEA may not interrupt sympathetic activities to the adrenals since these glands receive preganglionic, autonomic innervation. Hence, sympathetic outflow may cause a release of epinephrine and a secondary pressor effect. Whether or not this theorizing is correct, the fact remains that TEA in certain doses is capable of producing a pressor response in normal animals.

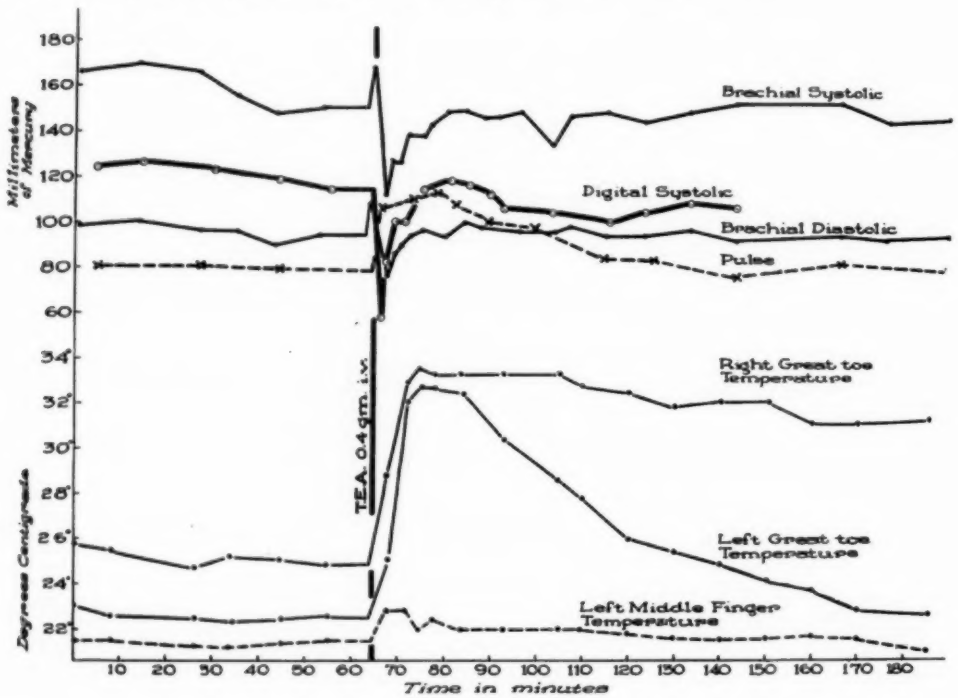


Fig. 5.—Changes in blood pressure, pulse rate, and digital temperature produced by the administration of TEA to a 43-year-old white female patient with Raynaud's disease and hypertension. This patient had had a bilateral lumbar sympathectomy in 1934 for hypertension.

The action of TEA on cardiac function has been studied both in the isolated heart and in the intact animal. Acheson and Moe[14] using a heart-lung preparation observed that the drug produced an increase in cardiac output especially in the failing heart and concluded that TEA has a positive inotropic effect similar to that of the cardiac glucosides.

In man, a tachycardia has been quite uniformly observed following the administration of TEA, and this change has been attributed to a blockade of the vagus inhibitor impulses to the heart.[2,4] Actually some investigators[15] have probably failed to recognize the magnitude of this tachycardia because their observations were made on patients who already had an abnormally high pulse rate (100 to 140 per minute) at the time TEA was given. In our normal subjects where care was taken to obtain a basal condition before giving the drug, the

pulse rate increased from 26 to 113 per cent with a mean increase of 56 per cent. It would be expected that both the positive inotropic effect and the tachycardia would produce an increase in cardiac output. Lyons and his associates[2] have observed an increase in cardiac output of 20 per cent with the administration of tetraethylammonium. However, these workers also suggest[4] that this change in cardiac output probably causes no great variation in blood pressure, at least not sufficient to interfere with the use of the change in blood pressure as an index of the release of vascular tone in patients with hypertension.

The measurement of both brachial and digital blood pressure proved to be of particular value in a study of the relative effectiveness of this increase in cardiac output and the decrease in vascular tone in producing the observed changes in blood pressure. The changes produced by the action of the TEA ion on the heart tend to elevate the blood pressure while peripherally the effects produced by the drug act to lower the blood pressure. The resultant change in blood pressure should be the algebraic sum of these two opposite effects at the particular level of the arterial tree where the pressure is measured. The cardiac pressor effect would be expected to be more evident at the level of the brachial artery while the peripheral depressor effect should be more pronounced at the level of the digital artery. Thus it is conceivable that a rise in pressure could occur in the brachial artery in response to the administration of TEA while a fall occurred in the digital artery. These changes were actually observed in two of the twenty control subjects (Fig. 1,*C*). However, in the majority of subjects the pressures at the two levels either rose or fell, but the dual effect on blood pressure was still evidenced by an increase in the brachial-to-digital pressure gradient. The consistent increase in gradient (Fig. 2) was produced by either a greater rise in brachial pressure or a greater fall in digital pressure. The particular type of response elicited by TEA will be determined by the degree of basal autonomic tone regulating both the heart rate and the state of constriction of the peripheral vessels, and also by the effectiveness with which the autonomic activity to each of these effector areas is interrupted. In any case it seems evident that the effects of TEA on the driving head of pressure cannot be ignored, especially when the pressure is measured at the level of the brachial artery.

Figure 6 is presented to demonstrate the importance of a tachycardia in maintaining the driving head of pressure when TEA is administered. This figure shows the blood pressure, pulse rate, and skin temperature changes produced by the administration of 300 mg. of TEA to a 61-year-old white male patient who had clinical evidence of advanced peripheral arteriosclerosis and hypertension of the arteriosclerotic type. The fact that an enormous fall in systolic blood pressure occurred in this patient when the drug failed to produce the usual tachycardia, suggests that tachycardia is ordinarily an important factor in the maintenance of the blood pressure. The basis for the absence of a tachycardia in this patient is not evident. The blood pressure effect here reflects only the decrease in peripheral resistance and therefore falls greatly. It is interesting to note that the type of blood pressure change observed in this patient is said to be the one more likely to be correlated with a good result following sympathectomy,[4,16] yet this patient displayed no evidence of increased vasomotor

tone and all clinical findings suggested that the hypertension was of the arteriosclerotic type which would, in all probability, respond poorly to surgery. It has been noted frequently that the blood pressure fall in this older age group is great.[2,3,5]

It is worthwhile in passing to point out the effects of this fall in blood pressure on the peripheral circulation. Skin temperatures of the left great toe and left third finger actually fell when the drug was administered (Fig. 6). The tempera-

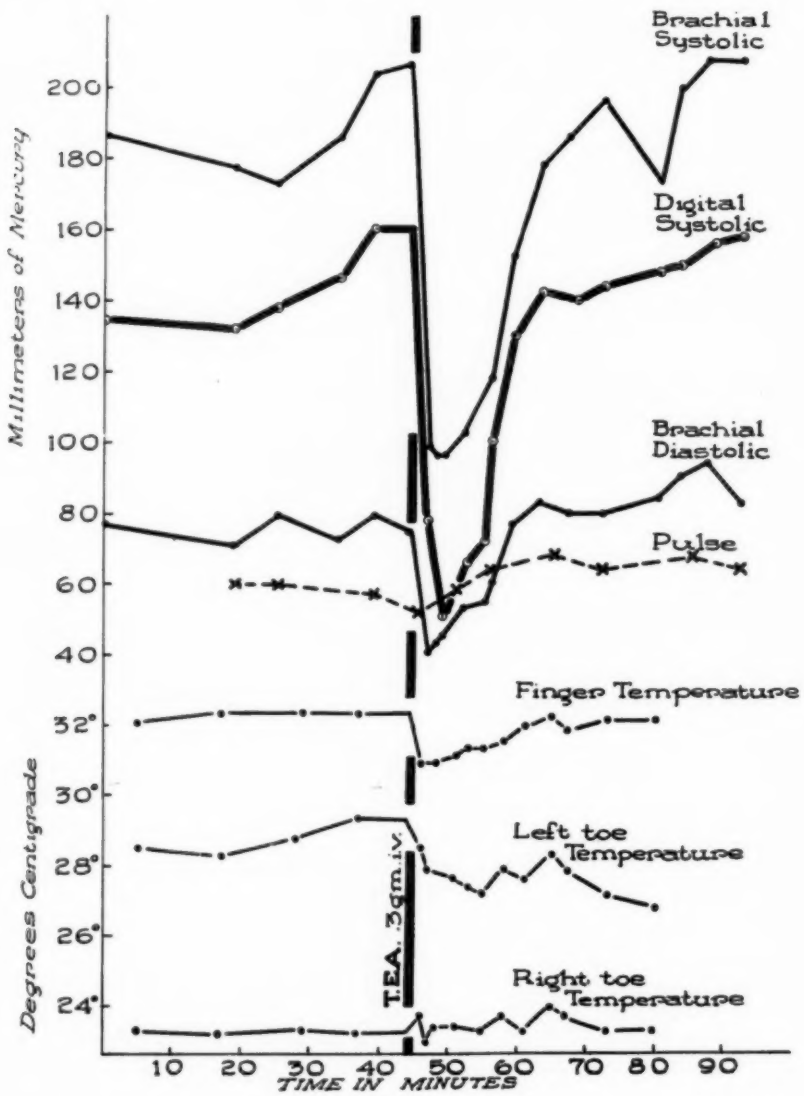


Fig. 6.—Blood pressure, pulse rate, and digital temperature changes following the administration of TEA to a 61-year-old white male patient with advanced peripheral arteriosclerosis and a hypertension of the arteriosclerotic type. An enormous fall in blood pressure occurred in the absence of the usual tachycardia.

ture of the great toe of the patient's right foot in which he had severe ischemic rest pain was unaltered. However, the temperature of this toe was already so close to that of the room that a further decrease in blood flow could not have altered its temperature significantly. Nevertheless, there was a striking increase in pain in this foot when the drug was given. These observations demonstrate that TEA produced a definite decrease in peripheral blood flow secondary to a marked fall in blood pressure. A run-off phenomenon was in operation causing a diversion of blood away from the partially obstructed vascular supply of the extremities into the dilated visceral vascular bed, as well as into the unobstructed portions of the peripheral vessels. The fall in blood pressure presumably was due to a generalized vasodilatation and fall in peripheral resistance which was not compensated by the usual tachycardia. In a purely occlusive vascular disease such as this, the administration of a drug which produces a generalized vasodilatation may add further circulatory embarrassment to the involved extremity by decreasing the driving head of pressure. The changes observed in this case emphasize that the drug must be used with caution in elderly patients.

4) *Abnormal Conditions.*—The presence of occlusive vascular disease will, of course, decrease the response of the blood flow to tetraethylammonium. The use of TEA as a diagnostic tool to evaluate the occlusive factor in vascular insufficiency is based on this impaired response.

In the presence of hypertension on a humoral basis the depressor effect of TEA may be minimal as in patients with pheochromocytoma. Conversely it has been suggested that in the presence of a neurogenic hypertension the fall in blood pressure produced by TEA may be unusually great.[4,10] It has been hoped that the change in blood pressure might be of assistance in evaluating the neurogenic element of hypertension.

We have demonstrated that there are several important factors which are unrelated to any cardiovascular pathology and yet are capable of altering the response to tetraethylammonium. A very wide degree of variability of response was observed in the normal subjects. The factors responsible for this variability will naturally interfere with the use of TEA as a diagnostic tool to evaluate the occlusive component of peripheral vascular disease or the neurogenic element of hypertension. Nevertheless the relative simplicity of this test probably justifies its use if as many variables as possible are controlled and if the limitations of the test are realized in interpreting the results.

SUMMARY AND CONCLUSIONS

1. Brachial and digital blood pressures, pulse rate, electrocardiograms and digital skin temperatures were observed following the administration of tetraethylammonium chloride to twenty normal subjects.

2. While the drug produced either a rise or fall or no change at all in brachial pressure, the pressure at the digital level decreased quite consistently, thus resulting in a significant increase in the pressure difference between these two levels of the arterial tree.

3. There was a consistent increase in heart rate varying from 26 to 113 per cent above the basal level.

4. Minor electrocardiographic changes were most pronounced in Lead III where the T waves became depressed or inverted.

5. The amount of rise of finger temperature varied greatly but the elevation in toe temperature was more consistent and persistent.

6. Three mechanisms are discussed which are probably responsible for the marked variability in the effects of TEA in normal subjects. These are: 1) individual differences in basal autonomic tone; 2) variability in the degree of blockade of the autonomic ganglia, and 3) various sites of action of TEA. The effects of TEA on several patients with cardiovascular disease were described in order to demonstrate that these three factors may be more significant than the underlying pathology in determining the type of response to TEA.

7. Evidence is presented suggesting that TEA is less effective in producing autonomic ganglion blockade in individuals when autonomic tone is high and in local areas with high tone.

8. It is proable that TEA should be placed in the category of competitive inhibitors since its blockade action appears to depend on its ability to inhibit acetylcholine by competition at the autonomic synapse.

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THE VALUE OF MINIATURE RADIOGRAPHY IN THE DETECTION OF HEART DISEASE

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THE primary purpose of the mass miniature x-ray surveys has been the detection of pulmonary tuberculosis. Their value in tuberculosis is well known and their usefulness in detecting other non-tuberculous pulmonary conditions is becoming more apparent. Their importance in the discovery of heart disease has not been fully utilized and only a few series[1,2] have been published in which an attempt has been made to assess the actual value of this method of case finding.

Because of the educational campaigns of Tuberculosis Organizations, the public is definitely aware of tuberculosis. A large number take advantage of the free, easily available chest x-rays without being referred by their physician. To most patients cough, sputum, dyspnea, pain in the chest, and hemoptysis are attributed to the respiratory and not to the cardiovascular system, although the latter is probably more frequently the cause of these symptoms. If the films are used only to detect tuberculosis many patients with heart disease would receive a negative report which they assume to mean that there is nothing organically wrong. They therefore delay seeking aid until their symptoms force them to do so, and if they are engaged in strenuous occupations they might do themselves considerable harm by continued effort.

For this reason a short preliminary survey was attempted to demonstrate the value of the miniature film in the detection of heart disease. During the months of December, 1948 and July, 1949 all 4- by 5-inch films taken at the Vancouver Unit of the Division of Tuberculosis Control of British Columbia were examined for abnormal cardiovascular shadows. Patients whose films were suspicious were asked to return for further study. Every person who was recalled was given a clinical examination, and a 14- by 17-inch film was taken. Fluoroscopy and electrocardiograms were done when indicated. The results are listed in Table I.

From a total of 7,093 films, 158 were selected as showing abnormal cardiovasculars pattern. Ninety of these were found to have definite heart disease. The types of heart disease were hypertensive cardiovascular disease (42), arteriosclerotic (15), rheumatic heart disease (26), congenital heart disease (6), and thyrotoxic heart disease (1). Thirty-three patients were unaware of existing heart disease and a number of others who knew of their lesion did not attribute their present symptoms to it. In the same period only twenty-two cases of tuberculosis were discovered; thirteen active and nine apparently arrested.

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Sixty-eight of those recalled had no evidence of heart disease. Several causes were responsible for this high percentage of error. Allowance must be made for the greater distortion at the distance of 48 inches from the x-ray tube focus as against 60 inches. Pregnancy and sthenic build with a high diaphragm made

TABLE I. RELATIVE INCIDENCE OF HEART DISEASE AND PULMONARY TUBERCULOSIS

Total Examined	7,093	
Patients Recalled	158	
No Heart Disease	68	
Definite Heart Disease	90 (1.27%)	
Hypertensive Cardiovascular Disease		42
Arteriosclerotic Heart Disease		15
Rheumatic Heart Disease		26
Congenital Heart Disease		6
Thyrotoxic Heart Disease		1
Patients Whose Cardiac Lesion Was Unknown to Them	33	
Tuberculosis Discovered in Same Period	22	
Minimal Active		3
Minimal Apparently Arrested		7
Minimal Apparently Cured		2
Moderately Advanced Active		3
Far Advanced Active		4
Primary		3

the heart appear enlarged in the miniature films. Scoliosis and a depressed sternum caused a deceptive appearance of enlargement. With increasing experience and more careful study of the films, a much greater accuracy is possible.

DISCUSSION

During the brief period of this study, the number of cases of heart disease found was four times that of tuberculosis. Although a patient with heart disease is not a public health menace early case finding is of increasing importance. The advances in the surgical treatment of congenital heart disease makes early detection essential. Earlier recognition of the rheumatic and degenerative types of heart disease and proper advice and treatment may prolong life expectancy. A number of those who were unaware of their cardiac lesion were engaged in strenuous occupations, and it is this group who can be aided by a change of employment which is compatible with their cardiac limitations.

These findings indicate that the mass chest x-ray survey is an excellent method of case finding in heart disease as well as in tuberculosis. It is important that all available clinical information which can be obtained from the miniature film be utilized and that the patient be referred for proper treatment for any abnormality which may be discovered.

The authors are indebted to Drs. W. H. Hatfield, G. F. Kincade and G. F. Strong for their help in carrying out this survey.

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NEW AIDS IN THE DIAGNOSIS OF DEXTROCARDIA

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TO MOST physicians the word dextrocardia brings to mind an anomaly of the heart which is associated with situs inversus of the abdominal viscera and which is often used by whimsical house staffs to trap unwary students and clinicians on ward rounds. Considerably less familiar than the classical type of dextrocardia are those types that are not associated with situs inversus of the abdominal viscera and are thus termed *isolated*.

Of the several available classifications of congenital dextrocardia one of the simplest and most widely quoted is that by Mandelstamm and Reinberg.[1] These authors recognized three main types: I. that which is associated with complete or partial situs inversus of other viscera; II. that which is isolated, and which shows mirror-image inversion of the cardiac chambers; and III. that which is isolated, but which shows a normal relationship of the cardiac chambers.

Dextroposition of the heart due to intrathoracic disease or injury was included by the authors as a fourth type of dextrocardia. Since such displacement of the heart is not congenital in origin it lies outside the scope of the present study.

Dextrocardia associated with situs inversus (Type I) has been so thoroughly characterized that, if embryologic considerations are excluded, little controversy still centers around it. The situation is otherwise with regard to Types II and III. In Abbott's interesting but bizarre series of 1,000 cases of congenital heart disease[2] there were eight cases of Type III dextrocardia, all of which were complicated by a cardiac malformation. Lichtman[3] collected 159 cases of Types II and III dextrocardia from the literature to which he added two of his own. Thirty-six of the 161 patients were studied at autopsy; only three were definitely found to have no complications. The most frequently associated malformations at autopsy were septal defects and obstructive lesions of the pulmonary outflow tract. Rösler[4] went so far as to deny the existence of an uncomplicated case. In spite of such views, the literature contains numerous reports of patients with Type III dextrocardia with no discernible complication and who had no physical disability whatever.[5,6,7] Although the average age at death is usually placed at something less than thirty years, 29 per cent of Lichtman's patients survived past that age as did 23 per cent of the patients studied by Rösler. It seems probable that some

From the Laboratory of Physiological Hygiene and the Department of Medicine, University of Minnesota, and the Veterans Administration Hospital, Minneapolis, Minnesota. Published with the permission of the Medical Director, Veterans Administration, who assumes no responsibility for the opinions expressed or the conclusions drawn by the authors.

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patients do indeed have uncomplicated Type III dextrocardia, that they have a much better outlook than do the patients with complicated dextrocardia, and that they often have not been separable clinically from the latter.

It is apparent, therefore, that the identification of the various types of dextrocardia and of any associated congenital cardiac defects is of more than academic interest. In Type I dextrocardia, the prognosis is excellent unless modified by noncardiac disorders. In Types II and III dextrocardia, the outlook

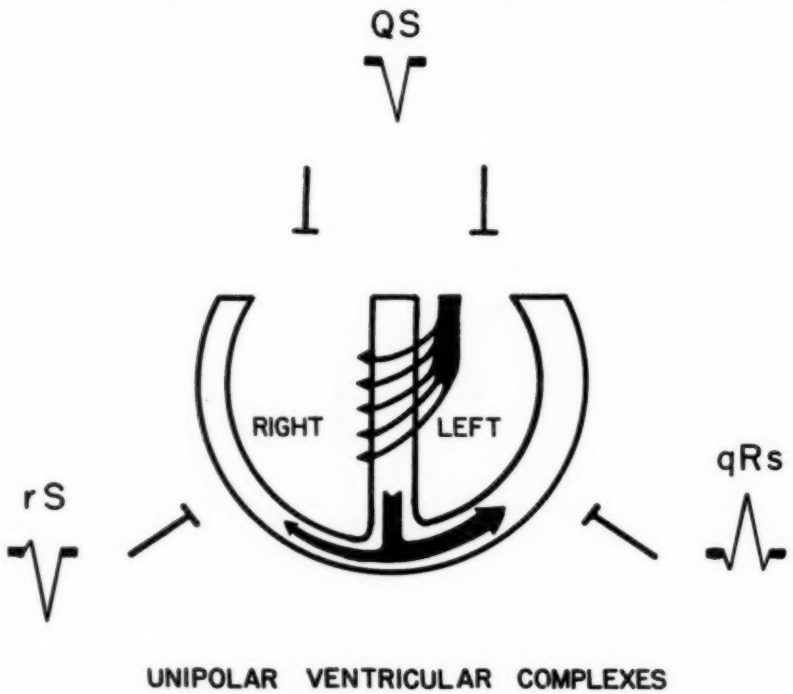

Fig. 1.—Schematic presentation of unipolar electrocardiographic patterns. The conduction of the impulse, first through the interventricular septum and then through the ventricular musculature, is represented by arrows.

is often determined by the nature of associated cardiac defects. For this reason if for no other, all appropriate diagnostic techniques should be brought to bear in order to achieve complete diagnosis. Since routine physical and roentgenographic techniques may not permit this, special methods may be required.

An indispensable aid in the identification of the various types of dextrocardia is the electrocardiogram, which provides information not only as to the position of the heart but also as to the arrangement of its chambers. The electrocardiogram in Type I dextrocardia presents the familiar mirror-image pattern in the limb leads. The precordial leads are reversed so that leads taken in orderly progression from a position just to the left of the sternum in the fourth intercostal space outward over the right side of the chest show the pattern usually seen in leads taken over the left side of the chest. The same pattern, including mirror-image inversion in the limb leads, may also occur in Type II dextrocardia

although little information is available on the topic. Similarly, electrocardiographic changes in congenital isolated dextrocardia (Type III) seem to have been insufficiently, and in some instances erroneously, described. Since there is no no inversion of the cardiac chambers a mirror-image electrocardiogram does not occur. Although reporting normal electrocardiograms in cases of this type, numerous authors[5,6,8] have presented tracings in which the T wave in the first limb lead was distinctly abnormal. In some instances it was merely flat but more often it was diphasic or inverted. Small Q waves were frequently present in one or more of the standard limb leads.

Unipolar electrocardiographic patterns are of particular interest in the diagnosis of dextrocardia. The technique, introduced by Wilson and his associates[9] and recently modified by Goldberger,[10] is extremely useful in defining the position of the heart. Figure 1 shows the electrocardiographic patterns ordinarily obtained when a unipolar electrode faces the epicardial surface of a ventricle or a ventricular cavity. Thus, when the electrode faces the outer surface of the left ventricle, a QRS deflection results; when it faces the outer surface of the right ventricle, an RS deflection is seen. A QS complex is ordinarily said to indicate that the electrode faces a ventricular cavity. In the classical type of dextrocardia (Type I) unipolar precordial leads are similar to bipolar precordial leads in that those taken over the right anterior chest correspond to those usually obtained over the left (Leads V_1 through V_6). The unipolar limb leads, as shown by Goldberger, are reversed, Lead V_R showing the pattern normally seen in Lead V_L. The left foot lead (V_F) is said to face the epicardial surface of the right ventricle and hence shows an RS or RSR′ pattern and an upright T wave. Unipolar patterns in other types of dextrocardia have been studied by Alzamora Castro.[11] The patterns observed by him in Type III dextrocardia are quite similar to those obtained by Goldberger in patients with pronounced counter-clockwise rotation of the heart around its long axis. Such rotation brings the left ventricle into a substernal position and carries the right ventricle to the right and posteriorly. Most of the unipolar precordial leads thus come to face the epicardial surface of the left ventricle and a prominent R wave is seen in the V leads nearest the left sternal margin. The T wave is upright. The left scapular lead (and the left arm lead) show QR patterns and inverted T waves, the latter feature being attributed by Goldberger to the fact that these leads face the posterior epicardial surface of the left ventricle. These and other features of the unipolar leads are summarized in Table 1.

TABLE I. UNIPOLAR ELECTROCARDIOGRAPHIC PATTERNS IN COUNTER-CLOCKWISE ROTATION OF OF THE HEART AROUND ITS LONG AXIS ACCORDING TO GOLDBERGER[10]

LEAD	QRS PATTERN	T WAVE
V_1	RS	Upright
V_{2-5}	QR	Upright
V_6	QR	Upright or inverted
Left scapular	QR	Inverted
Left arm	QR	Inverted
Right arm	QS	Upright
Left foot	R or RS	Upright

Another adjunct that may be useful in the diagnosis of some types of dextrocardia is the roentgenkymogram. This device, by clearly distinguishing between atrial and ventricular pulsations, often aids in the identification of the structures comprising the various margins of the cardiac silhouette. This information in turn may permit definition of the anatomic position of the heart.

For the exact diagnosis of intracardiac shunts, certain valvular anomalies, and patent ductus arteriosus, the technique of right heart catheterization has recently been shown to be of great value.[12] Since, in some types of dextrocardia, so much depends on the presence or absence of associated congenital defects of the heart the use of catheterization of the right side of the heart may be indicated.

In the following two patients, these and other diagnostic methods were applied in order to arrive at a precise definition of the position of the heart and, in one of the patients, to resolve a difficult diagnostic dilemma.

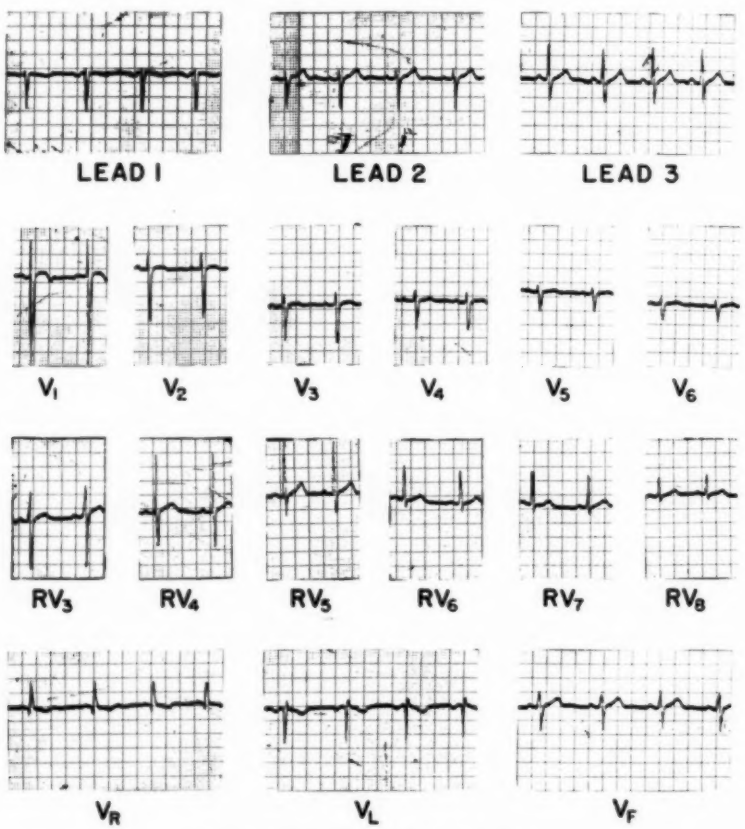

Fig. 2.—Electrocardiogram in Case 1.

CASE 1.—A 27-year-old white man was referred to the hospital because of a chronic, productive cough which had been present for at least fifteen years. He was not incapacitated but complained that the cough was increasingly productive of foul-smelling, yellow, purulent sputum.

A diagnosis of dextrocardia was made as a result of a routine physical examination when the patient was 17 years of age. He served in the Army Air Corps from 1943 to 1945 but was finally discharged because of "asthma."

Physical examination revealed a well-developed, well-nourished young man who did not seem to be ill. The temperature was 98.6°, the pulse and respiratory rates were normal, and the blood pressure was 120/72. There was a moderate amount of purulent exudate over the middle and lower turbinates. The thorax was symmetrical and expanded well. There was slight dullness to percussion over the lower posterior portion of the right hemithorax and in the same area coarse, moist râles and harsh breath sounds were heard. The area of cardiac dullness lay to the right of the midline but did not appear to be enlarged. The cardiac sounds were maximal in the fourth right intercostal space about 4 cm. from the midline. The rhythm was regular and there were no murmurs. In the abdomen, the liver was percussed in the left upper quadrant and an area of tympany was detected in the right upper quadrant. In the standing position, the right testicle was lower than the left. There was no clubbing of the digits or significant lymphadenopathy.

Routine examination of the blood, urine and stools disclosed nothing unusual. A culture of the sputum showed nonhemolytic Staphylococci and *Streptococcus viridans*. X-ray films of the chest showed that the heart shadow was to the right of the midline but was normal in size and shape. Accentuated pulmonary markings were also noted. Bronchograms disclosed minimal dilatation of one of the right posterior basilar branches. Films of the nasal sinuses supplied evidence of severe pansinusitis and diffuse osteitis around the frontal sinuses. X-ray examination of the gastrointestinal tract showed that the stomach lay to the right and the cecum to the left of the midline.

In the electrocardiogram (Fig. 2), a typical mirror-image inversion pattern was present.

Symptomatic treatment was instituted. For several weeks the patient produced about 100 c.c. of purulent sputum daily. Postural drainage and full doses of penicillin had no appreciable effect on the amount of sputum produced. The use of aureomycin, however, very quickly reduced the daily sputum production to about 20 c.c. of clear, odorless material. Additional bronchograms were suggestive of minimal bronchiectasis in the left middle lobe but the changes were not marked. Because of the pronounced improvement on chemotherapy and the minimal bronchographic evidence of bronchiectasis, surgical treatment of the pulmonary disease was considered inadvisable. At the time of discharge the patient was entirely free of symptoms.

The diagnoses were: dextrocardia, Type I, with complete situs inversus; chronic bronchitis; bronchiectasis; chronic pansinusitis.

CASE 2.—A 21-year-old male university student was first seen at the Laboratory of Physiological Hygiene in September, 1947, when he volunteered to serve as a normal control subject in a long-range study of cardiovascular degeneration. Careful questioning at that time did not disclose any complaints. An electrocardiogram showed a deeply inverted T wave in the first limb lead and a prominent Q wave in the third. The P waves were upright in all leads and the axis was normal. Further investigation was not carried out at that time but a year later, a second electrocardiogram proved to be exactly similar to the previous tracing. Roentgenologic studies suggested an anomalous position of the heart and the patient was referred to the Minneapolis Veterans Hospital for further study.

The past history did not disclose any evidence of significant illness. He had always been physically active and served in the Army without difficulty from April, 1946, to May, 1947.

The family history disclosed nothing of diagnostic interest.

Physical examination revealed a well-developed, well-nourished young man who seemed to be in good health. The temperature, pulse and respiratory rates were within the normal range. The blood pressure was 138/80. Nothing abnormal was detected in the head and neck. There was slight kyphosis and scoliosis with the convexity to the left in the upper thoracic region but the chest was not noticeably asymmetrical. The lungs were clear throughout. No cardiac pulsations were visible and no thrills could be felt. Percussion showed that the borders of cardiac dullness were 4 cm. to the left of the midsternal line in the third intercostal space, and 6 cm. to the right in the third and fourth intercostal spaces. The heart sounds were of normal quality and were loudest just to the right of the sternum in the third intercostal space. There was a Grade I systolic murmur over the lower portion of the area of cardiac dullness. A Grade II systolic murmur was audible in the second intercostal space to the left of the sternal margin. No diastolic murmurs were present. The edge of the liver was barely palpable in the right upper quadrant and the left

upper quadrant was tympanitic. The spleen could not be felt. There was no cyanosis, lymphadenopathy or clubbing of the digits.

Laboratory studies were all within normal limits.

X-ray studies of the chest confirmed the presence of slight upper thoracic kyphosis and scoliosis with the convexity to the left. The lung fields were clear. The cardiac shadow was globular in shape and possessed no clearly defined apex. Most of the shadow lay to the right of the midline (Fig. 3). There was no evidence of general or local enlargement in the posteroanterior or anterior oblique views although the pulmonary vessels were somewhat prominent, especially on the right. The arch and descending portion of the aorta lay to the left. The esophagus and

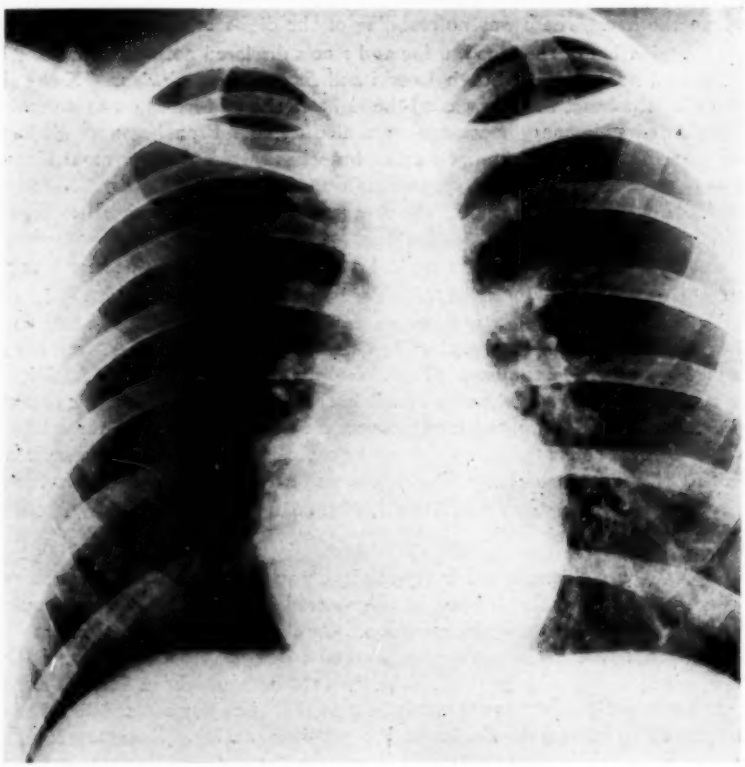

Fig. 3.—Six-foot teleroentgenogram in Case 2.

mediastinum were not displaced. A roentgenkymogram (Fig. 4) revealed that the right border of the cardiac silhouette was made up almost entirely of ventricular pulsations. Atrial pulsations formed the uppermost portions of the right and left cardiac margins. There were no unusual hilar pulsations. Fluoroscopy confirmed the findings already described.

The electrocardiogram was identical to that taken a year previously. The P waves were upright in all the standard limb leads. The T wave in the first limb lead was still inverted and Q_3 was still prominent although deep inspiration caused a decrease in its amplitude. In the unipolar chest leads the highest R wave was obtained just to the left of the sternum. It then progressively decreased in amplitude as the electrode was moved laterally. These and other electrocardiographic leads are presented in Figure 5. In addition to the leads shown in Fig. 5, a lead taken over the third thoracic vertebra showed a QR pattern and an inverted T wave. A right scapular lead showed a QS complex of low amplitude. The mean QRS axis was +31.7 and the mean T axis +141.5 degrees.

For diagnostic purposes cardiac catheterization was carried out. The catheter was passed with ease until it reached a position which, in the normal subject, corresponds to the right atrium. A pressure tracing at this point (Fig. 6) showed the catheter to be in the right ventricle, and further exploration disclosed that in order to move from atrium to ventricle it was necessary to withdraw the catheter to the uppermost portion of the right cardiac margin. Thence, with its tip pointing posteriorly, the catheter passed caudad and dorsally, instead of caudad, ventrally, and to the left as in the normally placed heart. Once in the ventricle, the catheter was confinde

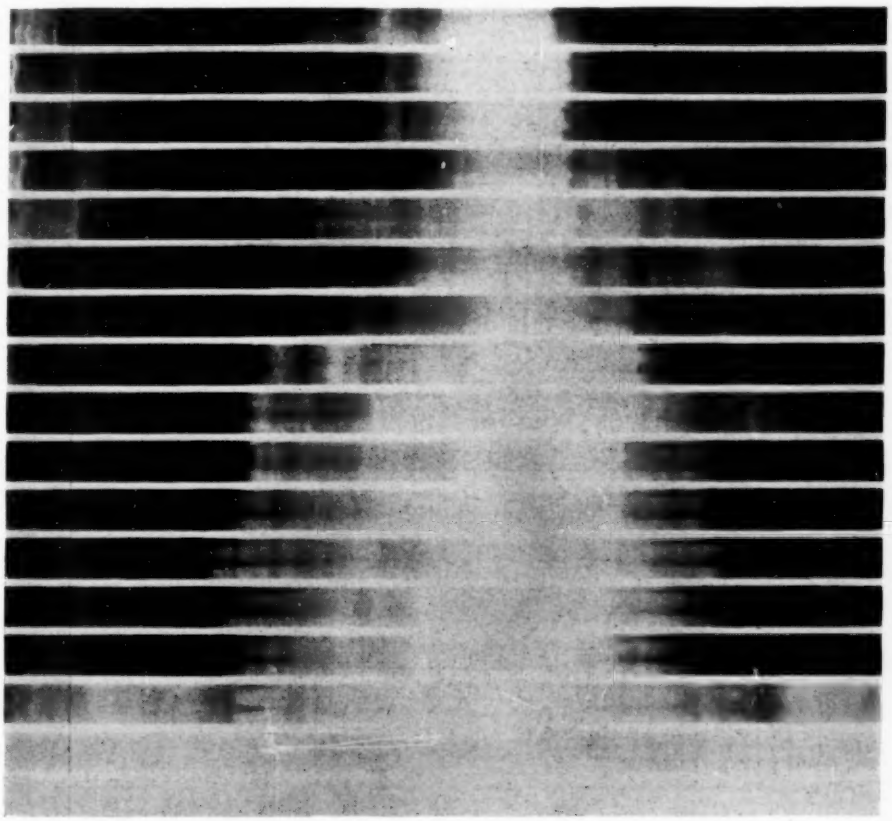

Fig. 4.—Roentgenkymogram in Case 2, showing characteristic ventricular pulsations along most of the right cardiac border.

to the extreme right portion of the cardiac shadow presumably because of the rotated position of the interventricular septum. At no time was it possible to bring the tip of the catheter to the midline although the cavity of the right ventricle was explored at some length. Attempts to advance the tip of the catheter into the pulmonary artery were greatly handicapped because of the extremely confusing anatomic relationships and the effort was finally discontinued because of frequent premature beats. During the latter, violent ventricular pulsations were seen along the right cardiac margin. The oxygen content of blood from the right atrium was 15.40 volumes per cent and that of blood from the right ventricle was 15.72 volumes per cent. The arterial blood was 92.2 per cent saturated. The oxygen consumption was 345 c.c. per minute, giving a metabolic rate of +19.4 per cent. The cardiac output was 10.09 liters per minute (arteriovenous oxygen difference taken as 3.42 volumes per cent), and the cardiac index was 4.97 liters per square meter per minute. The right ventricular systolic and diastolic pressures were 36.7 and 9.6 mm.

Hg respectively and the right ventricular pulse pressure was 27.1 mm. of mercury. Comparable normal mean values are 25, 4, and 22.5 mm. Hg, respectively.[13]

The diagnosis was congenital isolated dextrocardia (Type III), without inversion of the cardiac chambers and unassociated with significant cardiac malformation.

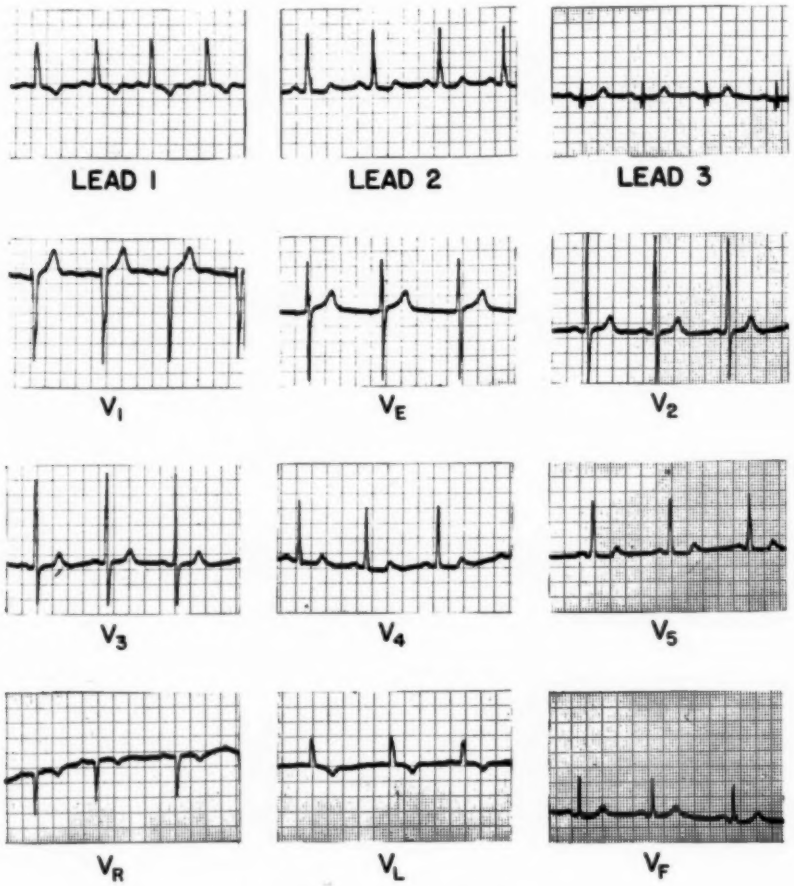

Fig. 5.—Electrocardiogram in Case 2.

DISCUSSION

Case 1 is typical in all respects of dextrocardia with situs inversus (Type I). The presence of sinusitis and bronchiectasis in addition to dextrocardia, a triad originally described by Kartagener,[14] is of interest, especially since the symptoms of respiratory disease caused the patient to seek hospitalization.

Case 2 stands in sharp contrast to Case 1. The patient had no complaints whatever and had unconditionally passed numerous physical examinations. The physical findings, even when a cardiac anomaly was suspected, were more confusing than helpful. The configuration of the cardiac silhouette was not

thought to conform to any of the usual patterns but the roentgenkymogram supplied a most important bit of evidence in disclosing ventricular pulsations along the right cardiac margin (Fig. 4). This finding suggested that the right ventricle was rotated to the right and posteriorly. Abundant confirmation of this conception of the position of the right ventricle was provided by right heart catheterization (Fig. 6). Unipolar electrocardiograms established the fact that

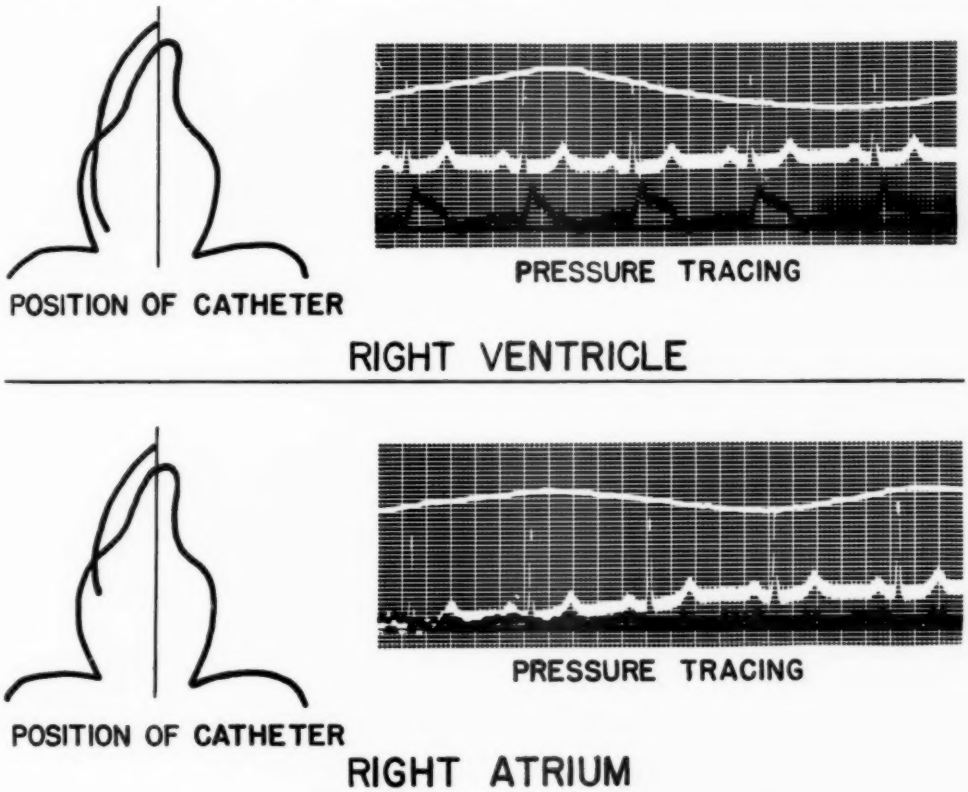

Fig. 6. Pressure tracings obtained by catheterization of the right side of the heart in Case 2.

the left ventricle lay more anteriorly than usual. The R wave, which was highest in Lead V_2 and progressively declined in Leads V_3 through V_6, indicated that over most or all of the distance (Leads V_2 through V_6) the exploring electrode faced the epicardial surface of the left ventricle. Lead V_L and the left scapular leads, with their R complexes and inverted T waves, probably indicated that in each instance the electrode faced the posterior surface of the left ventricle. If Goldberger's views are correct, the absence of the Q wave ordinarily seen in both these leads is of great interest since this feature should help to identify the position of the interventricular septum. The excitation of the interventricular septum proceeds from left to right, as shown in Figure 7. In unipolar electrocardiography the initial deflection of the QRS complex is usually taken to be a record of septal

excitation. If this be true, the direction of the initial deflection will be determined by the relative positions of the electrode and of the interventricular septum itself. The various possibilities are illustrated in Fig. 7, from which it can be seen that under some circumstances an electrocardiographic record of septal excitation may be entirely absent. In Case 2, since the left scapular and the left arm leads contained no Q wave, the septum appears to have been located approximately parallel to a line drawn diagonally across the chest cavity, from the

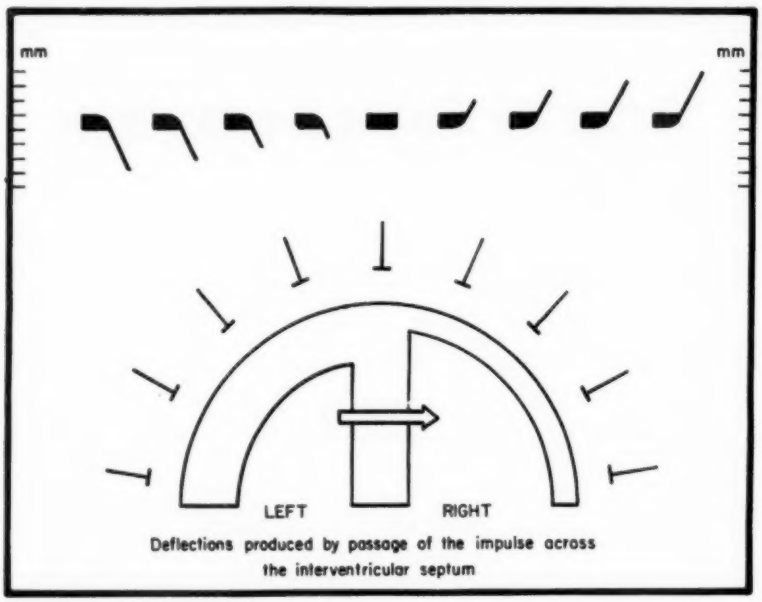

Fig. 7. Diagram illustrating how changes in position of the unipolar electrode may affect the initial deflection of the QRS complex.

fourth right intercostal space at the sternal margin to the mid-point of the spine of the scapula. The other unipolar limb leads were consistent with this interpretation. Lead V_R showed a QS complex instead of the usual RS pattern, a finding usually taken to indicate that the exploring electrode faces a ventricular cavity. Lead V_F showed a simple R configuration due to the fact that the exploring electrode faced the epicardial surface of the left ventricle. It was quite similar to V_5 and V_6, in which positions the exploring electrode also faced the epicardial surface of the left ventricle.

The anomalous position of the heart was thus made reasonably clear by the roentgenologic and electrocardiographic evidence. Neither technique, however, could exclude the presence of a complicating malformation. Catheterization of the right heart was of crucial importance in this regard. The absence of a significant difference between the oxygen content of the blood samples taken from the right atrium and ventricle proved the absence of a functionally important shunt through the interventricular septum and rendered such a shunt through the interauricular septum very unlikely. Dexter and co-workers[12] have shown

that differences in oxygen content of blood taken from the right atrium and from the right ventricle may be as high as 0.9 volume per cent in the normal individual. In Case 2, the difference in oxygen content of blood taken from the two sites was 0.32 volume per cent, a value that is well within the normal range. Owing to the fact that the patient was quite anxious during the procedure, the metabolic rate and cardiac output were moderately elevated. Both the right ventricular systolic and diastolic pressures were slightly higher than the normally accepted values, a fact probably attributable to the unusual position of the right chambers of the heart with relation to the standard reference level used for pressure measurements. The pulse pressure in the right ventricle was within the normal range, thus excluding pulmonic stenosis.

The evidence obtained indicated that the case presented was representative of Type III dextrocardia since the anomaly was congenital, isolated, and was not associated with inversion of the cardiac chambers. In the absence of concomitant cardiac malformations, the outlook for the patient was thought to be good.

SUMMARY

The use of new diagnostic techniques in the identification of two types of dextrocardia is discussed. Of the two cases presented, one showed mirror-image dextrocardia associated with situs inversus, sinusitis, and bronchiectasis (Kartagener's Triad). The other was an example of uncomplicated congenital isolated dextrocardia. Careful investigation of the latter patient by standard diagnostic methods, roentgenkymography, catheterization of the right side of the heart, and particularly by unipolar electrocardiography disclosed that the heart lay mostly to the right of the midline and that the left ventricle was substernal in position while the right ventricle lay posteriorly. The stomach and liver were in their usual positions. Inversion of the cardiac chambers and functionally significant cardiac malformations were excluded largely on the basis of evidence obtained by electrocardiography and by catheterization of the right side of the heart.

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NORMAL RESPIRATORY VARIATION OF CYCLE LENGTH, Q-T INTERVAL, AND CORRECTED Q-T INTERVAL OF THE ELECTROCARDIOGRAM

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THE duration of ventricular systole is known to increase or to lose the ability to decrease with increased heart rate, in certain pathological conditions such as anatomical cardiac damage, congestive cardiac failure, and rheumatic myocarditis.[1,2,3,4,5]

Since the duration of electrical systole (Q-T interval) is proportional to the cycle length,[6] Bazett's formula[7] for a corrected Q-T interval ($Q\text{-}T_c$) is frequently used. $Q\text{-}T_c$ is obtained by dividing the Q-T interval in seconds by the square root of the corresponding cycle length in seconds. Cheer and Dieuaide[2] report that $Q\text{-}T_c$ was below 0.400 in 200 normal adults (100 men, 100 women) and above 0.400 in 200 adults with congestive heart failure or anatomical heart damage. Taran and Szilagyi state that in the quiescent rheumatic child $Q\text{-}T_c$ fell below 0.405, whereas in active rheumatic myocarditis $Q\text{-}T_c$ was above 0.405.[5]

Shipley and Hallaran[8] have already pointed out that the R-R interval of the electrocardiogram (cycle length) varies greatly in sinus arrhythmia but that the Q-T interval remains remarkably constant, and therefore an average R-R should be used in the calculation of $Q\text{-}T_c$.

It seemed desirable also to investigate the effects of respiration on the $Q\text{-}T_c$.

METHOD

Records of 24 normal adult male and 24 normal adult female subjects where the electrocardiogram had been recorded simultaneously with respiration were examined. The second lead was used in all cases, and the Q-T and R-R intervals were measured in beats that occurred at the peak of expiration and the peak of inspiration; a caliper was used in the same manner and with the same degree of accuracy that obtains in the ordinary usage of the electrocardiogram. $Q\text{-}T_c$ was computed with a slide rule that was accurate to three decimal places.

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Results

The individual respiratory variation of the cycle length, Q-T time, and Q-T_c is shown in Table I. Table II shows the total variation with inspiration of these same measurements. It is noteworthy that although the cycle length decreased by more than 0.01 second in inspiration in thirty-one subjects, the Q-T interval remained constant to within .01 second in thirty-three.

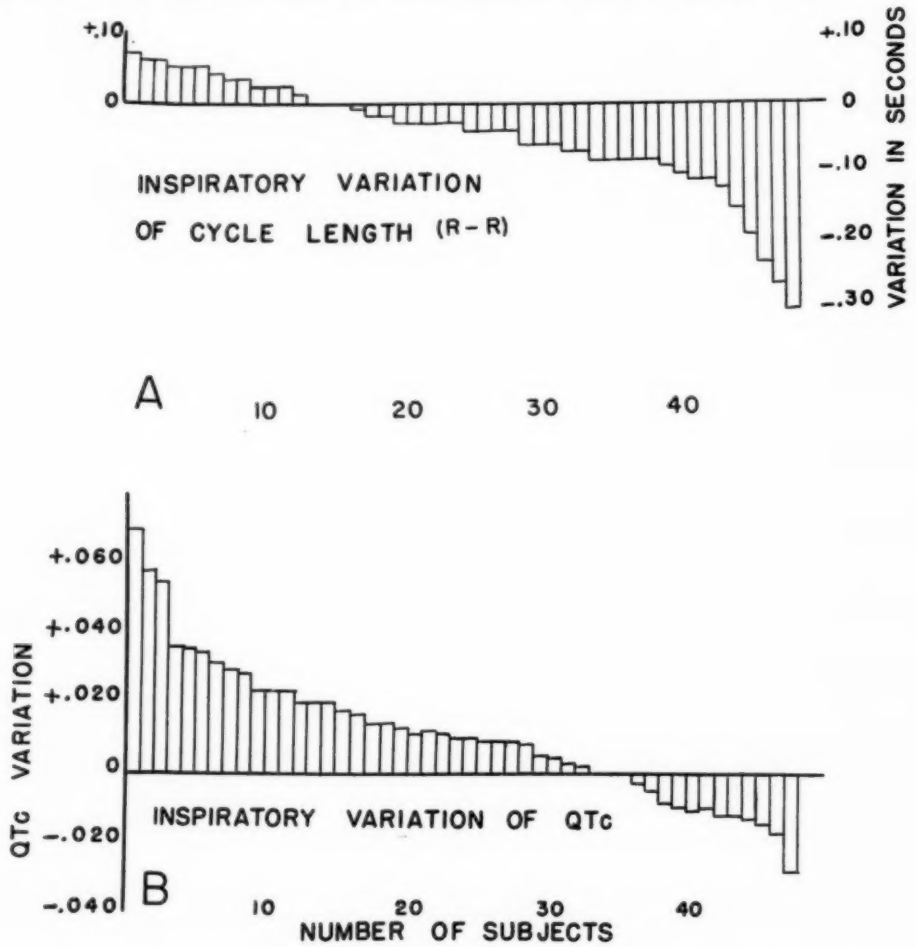

Fig. 1.—Each vertical bar represents one subject. In *A* is shown the inspiratory change of cycle length. The cycle length diminished more than 0.01 second in thirty-one subjects. In *B* is shown the inspiratory change of Q-T_c. In thirty-three subjects there was an increase with inspiration.

Q-T_c increased with inspiration in thirty-two subjects, decreased in twelve and remained the same in three. In six subjects Q-T_c exceeded 0.405; two in expiration only (Subjects 13 and 14); two in inspiration only (Subjects 3 and 8); and two in both inspiration and expiration (Subjects 1 and 10). Figure 1 is a graph of the inspiratory change of the cycle length and Q-T_c in the forty-eight subjects.

TABLE I. INDIVIDUAL RESPIRATORY VARIATION OF THE CYCLE LENGTH, Q-T TIME AND Q-T_c

SUBJECT	CYCLE LENGTH		Q-T TIME		Q-T_c	
	INSP.	EXP.	INSP.	EXP.	INSP.	EXP.
1	.68	.68	.34	.34	.413	.413
2	.81	.90	.35	.35	.389	.369
3	.76	1.0	.36	.36	.414	.36
4	.90	.93	.34	.34	.36	.35
5	.78	.78	.33	.33	.374	.374
6	.84	.94	.36	.35	.394	.363
7	.93	1.13	.36	.36	.374	.339
8	.82	1.12	.40	.37	.443	.353
9	.77	.80	.33	.34	.377	.38
10	.71	.79	.36	.37	.428	.416
11	.76	.8	.35	.35	.403	.391
12	1.34	1.47	.44	.44	.38	.363
13	.96	1.0	.37	.39	.385	.39
14	.82	.86	.36	.38	.397	.409
15	.89	1.08	.38	.36	.403	.346
16	.68	.76	.32	.36	.388	.416
17	.70	.76	.28	.29	.401	.332
18	.81	.77	.32	.30	.365	.342
19	.8	.87	.33	.32	.356	.368
20	.78	.79	.35	.34	.396	.382
21	.87	.84	.37	.36	.396	.393
22	.68	.63	.33	.29	.400	.365
23	.76	.87	.32	.33	.367	.354
24	.8	.73	.32	.32	.358	.375
25	.74	.8	.32	.32	.372	.358
26	.67	.73	.30	.32	.367	.375
27	.66	.64	.30	.28	.370	.350
28	.76	.74	.35	.33	.402	.384
29	.63	.74	.25	.28	.315	.325
30	.73	.76	.35	.34	.41	.390
31	.8	.74	.30	.30	.335	.349
32	.76	.86	.32	.35	.368	.377
33	.8	.88	.32	.33	.358	.356
34	.65	.77	.28	.28	.347	.319
35	.66	.66	.30	.30	.369	.369
36	.84	.90	.34	.33	.371	.348
37	.85	1.0	.32	.33	.347	.33
38	.59	.62	.28	.28	.365	.355
39	.84	.88	.36	.36	.393	.384
40	.66	.64	.30	.28	.370	.350
41	1.08	1.16	.39	.39	.373	.362
42	.86	.89	.32	.32	.345	.340
43	.76	.80	.30	.32	.344	.357
44	.78	.8	.33	.33	.374	.369
45	.68	.71	.28	.28	.340	.332
46	.63	.58	.28	.28	.358	.368
47	.8	.75	.32	.28	.358	.324
48	.74	.73	.33	.32	.384	.375

TABLE II. VARIATION WITH INSPIRATION

	Q-T_c	R-R	Q-T
Increased	33	12	8
Decreased	12	31	7
Same	3	5	33

Discussion

Since the cycle length usually decreases with inspiration, and the Q-T time tends to be constant, it is evident that the Q-T_c will usually increase with inspiration.

This respiratory variation is so frequent and so pronounced that if Q-T_c is to be used in the manner suggested by Taran and Szilagyi, for instance, where a Q-T_c over 0.405 indicates rheumatic myocarditis, and where serial measurements may be used as an indication of the progress of this disease, then it is important to measure both inspiratory and expiratory beats. Since the simultaneous recording of respiration and the electrocardiogram is not always feasible, it is suggested that measurements be made on the longest and shortest cycle lengths within a period of time that is certain to encompass one complete respiration.

Summary

1. The Q-T and R-R intervals were measured in both inspiration and expiration in forty-eight normal adults, and Q-T_c was computed for both.

2. Q-T remained constant in thirty-three subjects, R-R decreased with inspiration in thirty-three subjects, and Q-T_c increased with inspiration in thirty-three subjects.

3. It is suggested that both inspiratory (usually shortest) and expiratory beats (usually longest) be used in the calculation of Q-T_c.

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THE DURATION OF THE Q-T INTERVAL IN MYOCARDIAL INFARCTION

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THE Q-T interval of the electrocardiogram has been the subject of only a few sporadic clinical reports in the past three decades.[1-6] No investigation has been made upon a large series of electrocardiograms, especially in patients with myocardial infarction. Therefore this study was undertaken to demonstrate those changes in the duration of the Q-T interval which might occur during the course of this disease.

Several factors have contributed to the confusion and controversy concerning the actual clinical significance of the measurement of the Q-T interval of the electrocardiogram. In 1920, Bazett[7] and Fridericia[8] first demonstrated the relationship of the duration of "electrical systole" to the cardiac rate. Q-T interval and "electrical systole" have been used interchangeably for almost thirty years. It must be emphasized, however, that (1) systole is in reality a mechanical phenomena and (2) the Q-T interval is not the most accurate measure of the duration of systole.

It was for this reason that Katz[9] in 1921 relied upon heart sound tracings to measure variations in the duration of systole brought about by various physical and chemical changes in the circulation of dogs. However tempting it may be to use these terms synonomously, the duration of the Q-T interval of the electrocardiogram is merely a crude approximation of the duration of ventricular systole.

In spite of this, some investigators[1-6] have found definite prolongations of the Q-T interval (referred to as electrical systole) in various forms of heart disease, and Berliner[2] among others has demonstrated shortening of the Q-T interval with digitalis therapy. Dock[10] and White and his collaborators[11,12] on the other hand failed to find any significant changes.

Further confusion has been added in the attempt to find a suitable algebraic formula which would best express the relationship of the Q-T interval to the cardiac rate. All authors agree that the duration of systole varies with the cardiac rate and Schlamowitz[13] has attempted to correlate this curvilinear relationship mathematically. For the sake of completeness the various algebraic formulas are included in Table I.

Recently the work of Taran and Szilagyi,[6] on children with active rheumatic carditis, has revived the interest of clinicians with respect to the actual significance of the Q-T interval as an indication of myocardial integrity. Realizing, of course, the many physiological, pathological, and physiochemical factors that may

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TABLE I. FORMULAS USED TO CORRELATE THE DURATION OF ELECTRICAL SYSTOLE WITH THE CARDIAC RATE

AUTHOR	FORMULA	LEGEND
Bazett[7]	$S = K\sqrt{C}$	S = systole C = cardiac rate (cycle) K = 0.37 second for males, 0.40 second for females
Fridericia[8]	$S = 8.22\sqrt[3]{P}$	S = systole P = cardiac cycle
Chen[1]	$k = \frac{QT}{\sqrt{R\text{-}R'}}$	QT = systole R-R′ = cardiac cycle
Ashman[16]	Males $QT = 0.375 \log[10(C + 0.07)]$ Females $QT = 0.385 \log[10(C + 0.07)]$	QT = systole C = cardiac cycle
Schlamowitz[13]	$QT = 0.205C + 0.167$ or $K = \frac{QT + 0.167}{C}$	K = 0.205 C = cardiac cycle QT = systole
Taran and Szilagyi[6]	$QT_c = \frac{QT}{\sqrt{C}}$	QT_c = systole corrected for cardiac rate QT = systole measured C = cardiac cycle (seconds)

affect the duration of the Q-T interval, it was suspected that some specific alterations might occur as a result of the cardiac damage produced by acute myocardial infarction.

METHOD OF STUDY

The duration of the Q-T interval was measured from the first deflection from the isoelectric line following the P wave (the beginning of the Q wave, or R wave if Q wave was absent) to the point at which the T wave returned to the isoelectric line. At least five readings were made on each tracing, limb Lead II and Leads CR_2, CR_3, and CR_4 being the most suitable. Since simplicity of measurement was desirable, no attempt was made to differentiate any increment smaller than 0.01 second. For this study the author will employ the Taran and Szilagyi[6] modification of Bazett's formula because of its simplicity,

$$QT_c = \frac{QT}{\sqrt{R\text{–}R'}},$$

where QT_c is the Q-T interval corrected for cardiac rate or the equivalent of K in Bazett's formula, QT is the measured Q-T interval, and $R\text{-}R'$ is the length of a single cardiac cycle. All are expressed in seconds. Henceforth, also, the Q-T interval corrected for the cardiac rate will be referred to as QT_c. A table was prepared (Table II) in which QT_c was calculated for cardiac cycles (R-R′) vary-

ing from 0.40 to 1.20 seconds and measured Q-T intervals from 0.20 to 0.60 second, on the basis of the Taran and Szilagyi modification of Bazett's formula. In this table QT is given in increments of 0.02 second for simplicity. For the odd numbers suitable QT_c values may be interpolated. Since this table was prepared and these observations made, Kissin and co-workers[20] have published a nomogram by which QT_c may be obtained. This nomogram was based on Bazett's formula.

TABLE II. CALCULATIONS OF THE CORRECTED Q-T INTERVAL (QT_c) BY THE TARAN AND SZILAGYI MODIFICATION OF BAZETT'S FORMULA: $QT_c = \frac{QT}{\sqrt{R - R'}}$

R – R′ CARDIAC CYCLE	Q-T INTERVAL (MEASURED) SECONDS × 100																				
SECONDS × 100	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52	54	56	58	60
40	32	35	39	42	45																
42	31	34	37	40	43	47															
44	30	33	35	39	42	45	48														
46	29	32	35	38	41	44	47	50													
48	29	32	34	38	40	43	46	49	52												
50	28	31	33	37	40	42	45	48	51	54											
52	28	31	33	36	39	42	45	47	50	53	56										
54	27	30	32	35	38	41	44	46	49	52	55	57									
56	27	29	32	35	38	40	43	45	48	51	54	56	59								
58		29	31	34	37	39	42	45	47	50	53	55	58	60							
60		28	31	34	36	39	42	44	46	49	52	54	57	59	62						
62		28	30	33	36	38	41	43	46	48	51	53	56	58	61						
64		28	30	33	35	38	40	43	45	48	50	52	55	57	60						
66		27	29	32	35	37	39	42	44	47	49	52	54	57	59						
68		27	29	32	34	37	39	41	44	46	49	51	53	56	58						
70			28	31	34	36	38	41	43	45	48	51	53	55	57	60					
72			28	31	33	36	38	40	42	45	47	50	52	54	57	59					
74			28	30	33	35	37	40	42	44	47	49	51	53	56	58	60				
76			27	30	32	35	37	39	41	44	46	48	51	53	55	57	60				
78			27	29	32	34	36	39	41	43	45	48	50	52	54	57	59				
80			27	29	31	34	36	38	40	43	45	47	49	51	53	56	58	60			
82			27	29	31	34	35	38	40	42	44	46	49	51	53	55	57	60			
84				28	31	33	35	37	39	42	44	46	48	50	52	55	57	59			
86				28	30	33	35	37	39	41	43	45	48	50	52	54	56	58	60		
88				28	30	32	34	36	38	41	43	45	47	49	51	53	55	57	60		
90				27	29	32	34	36	38	40	42	44	46	49	51	53	55	57	59		
92				27	29	31	33	36	38	40	42	44	46	48	50	52	54	56	59		
94				27	29	31	33	35	37	39	41	43	45	47	50	52	54	56	58	60	
96				27	28	31	33	35	37	39	41	43	45	47	49	51	53	55	57	59	
98					28	30	32	34	36	38	40	42	44	46	48	51	53	55	56	59	
100					28	30	32	34	36	38	40	42	44	46	48	50	52	54	56	58	60
102					28	30	32	34	36	38	40	42	44	46	48	50	52	53	55	57	59
104					27	29	31	33	35	37	39	41	43	45	47	49	51	53	55	57	59
106					27	29	31	33	35	37	39	41	43	45	47	49	50	52	54	56	58
108					27	29	31	33	35	37	39	40	42	45	46	48	50	52	54	56	58
110						29	31	32	34	36	38	40	42	44	46	48	49	51	53	55	57
112						28	30	32	34	36	38	40	42	44	45	47	49	51	53	55	57
114						28	30	32	34	36	38	39	41	43	45	47	48	50	52	54	56
116						28	30	31	33	35	37	39	41	43	44	46	48	50	52	54	55
118						28	29	31	33	35	37	39	41	42	44	46	47	49	51	53	55
120						27	29	31	33	35	37	38	40	42	44	46	47	49	51	53	54

RESULTS

A total of 945 electrocardiograms was studied. Of these 117 represented normal electrocardiograms selected at random from the files of the Cardiac Station of the Jewish Hospital. The tracings were those of 82 men and 35 women varying from 16 to 60 years of age. The remaining 828 electrocardiograms were examined on the clinical records of 406 patients with myocardial infarction, so diagnosed on discharge from the Jewish Hospital from Jan. 1, 1941, to Dec. 31, 1946. Of these 406 patients, 224 were men and 122 women, the average age being 59.2 years, slightly lower for the men and higher for women. Six tracings were eliminated as unsuitable for study.

Normal Electrocardiograms.—Group 1 consisted of the normal electrocardiograms. In these the average QT_c was 0.397 second; 0.392 second in the case of 82 tracings taken on normal men, and 0.406 second on 35 tracings on normal women. In 80.9 per cent of the 117 tracings the QT_c varied from 0.38 second to 0.42 second inclusive. For comparison with normal figures of other authors Table III should be consulted.

TABLE III. NORMAL FIGURES FOR THE DURATION OF ELECTRICAL SYSTOLE (QT_c) IN MALES AND FEMALES

AUTHOR	NORMAL QT_c (SECONDS)			FORMULA USED
	MALE	FEMALE	AVERAGE	
Bazett[7]	0.37	0.40	0.385	Bazett
Dock[10]	0.3841	0.3890	0.391	Fridericia
Cheer[4]	0.3743	0.3877	0.381	Bazett
Taran and Szilagyi[6]			0.3924	Bazett
Author	0.392	0.406	0.397	Bazett

Acute Myocardial Infarction.—Group 2 included 556 electrocardiograms on persons with acute myocardial infarction of less than one month's duration, so far as could be determined from the clinical record. The average QT_c in this group was 0.448 second. Of the tracings in this group, 89.5 per cent revealed the QT_c to be 0.43 second or greater, the highest being 0.52 second.

Late Myocardial Infarction.—Group 3 consisted of 109 electrocardiograms made in patients with acute myocardial infarction one month or more following the onset of illness. The average QT_c in this group was 0.411 second. A majority (83.3 per cent) ranged from 0.39 to 0.43 second inclusive.

Digitalis Effect.—Group 4 represented tracings of persons with congestive heart failure due to acute myocardial infarction and, in some instances, other causes, to whom therapeutic doses of digitalis had been administered. This group revealed an average QT_c of 0.386 second, 79.5 per cent of these showed QT_c values of 0.40 second or less.

These figures were analyzed by the formula: $\sigma = \sqrt{\frac{\Sigma (X - X)^2}{n}}$ and all data were proved to be admissible. Figure 1 shows a composite distribution of all four groups.

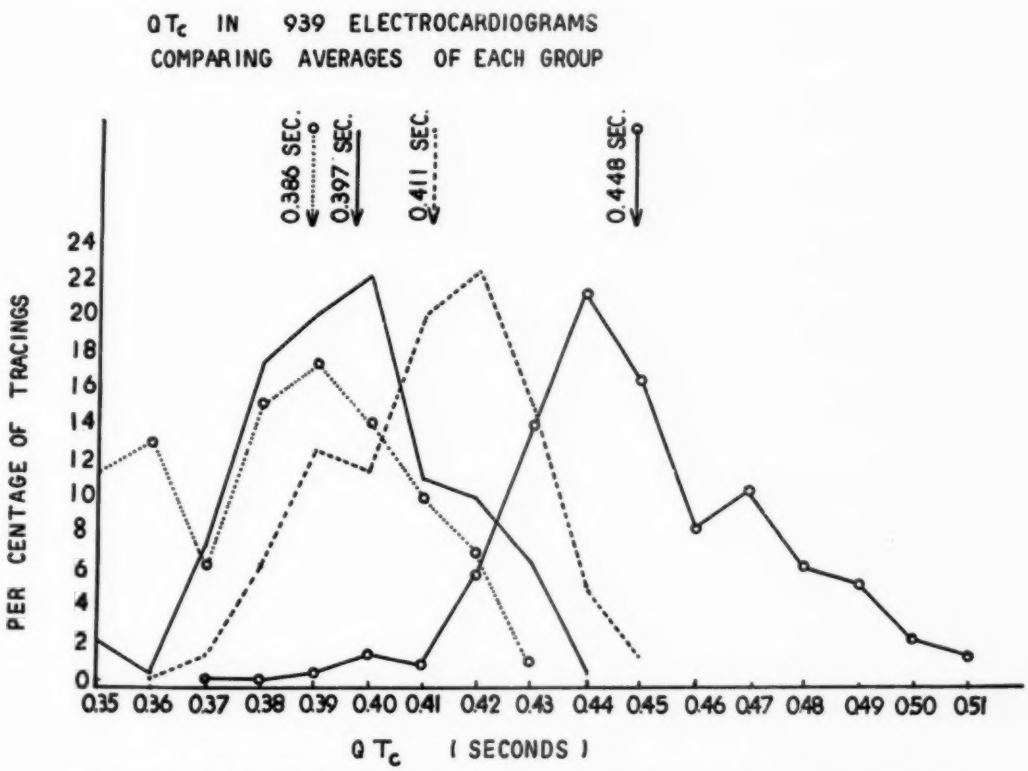

Fig. 1.—Composite distribution curves of QT_c values in Groups 1 to 4. Note prolongation in early group and relative shortening in group which had received digitalis. Actual time relations are seen in Fig. 2.

Group 1_____Normal, Group 2 o_____o Early, Group 3 _ _ _ _ _ _ Late, Group 4 o. . . . . o Digitalis.

Serial Electrocardiograms.—Group 5 consisted of 40 patients with 4 or more electrocardiograms taken during a single attack of myocardial infarction. The duration of illness was divided into six weekly periods and all QT_c values in each period averaged (Table IV). The results indicate a drop of QT_c from an average of 0.458 second during the first week of infarction to an average of 0.419 second during the sixth week. Although the week-to-week decreases do not vary significantly statistically, the drop from first to sixth week is statistically significant.

Relation of QT_c to the Electrocardiographic Localization of the Myocardial Infarction.—There were 567 tracings studied in which some definite localization of the myocardial infarction was given.* These were variously described as indi-

*Electrocardiograms were read by Dr. Alexander Margolies, Senior Attending Cardiologist, Jewish Hospital, Philadelphia.

cated in Table IV. The tracings were further divided weekly as with Group 5 and the average QT_c for each week noted (Table IV). During the early weeks of myocardial infarction these results clearly indicate that: (1) in electrocardiograms demonstrating a pattern of anteroseptal damage QT_c is prolonged more than the average; (2) in electrocardiograms demonstrating a pattern of posterior wall damage, QT_c is prolonged, but less than the average; (3) in electrocardiograms demonstrating a pattern of anterior-wall damage QT_c is prolonged almost equivalent to the average.

TABLE IV. QT_c VALUES OF ELECTROCARDIOGRAMS DEMONSTRATING THE VARIOUS PATTERNS OF ACUTE MYOCARDIAL INFARCTION DIVIDED INTO SIX WEEKLY PERIODS COMPARED TO AN AVERAGE FROM SERIATUM TRACINGS IN FORTY SELECTED PATIENTS*

ELECTROCARDIOGRAPHIC LOCALIZATION OF THE MYOCARDIAL DAMAGE	WEEK OF ILLNESS											
	1		2		3		4		5		6	
Anterior	0.450	(76)*	0.441	(48)	0.445	(37)	0.434	(28)	0.439	(22)	0.420	(29)
Antero-septal	0.465	(37)	0.462	(19)	0.471	(17)	0.451	(8)	0.455	(11)	0.416	(7)
Posterior	0.446	(52)	0.442	(25)	0.431	(22)	0.426	(14)	0.426	(9)	0.405	(20)
Postero-septal	0.452	(5)	0.452	(2)	0.463	(3)						
Lateral	0.420	(5)	0.440	(2)	0.415	(3)	0.430	(1)	0.420	(1)		
Antero-lateral	0.455	(9)	0.440	(9)	0.427	(6)	0.430	(3)	0.427	(4)	0.430	(1)
Postero-lateral	0.456	(11)	0.443	(3)	0.442	(4)	0.442	(4)	0.430	(2)		
Endocardial	0.470	(3)	0.400	(1)	0.390	(1)			0.380	(1)		
Through and through	0.440	(5)	0.455	(2)	0.420	(1)			0.400	(1)		
Average in 40 Cases	0.458	(42)	0.445	(35)	0.444	(28)	0.434	(25)	0.434	(29)	0.419	(29)

*Figures in parentheses are number of tracings examined in each group. For graphic comparison see Fig. 2.

After the fifth week all groups approach the average so that by the sixth week there is little or no significant difference in QT_c. These relations are indicated in Fig. 2. Since the standard error of mean in these groups varied from 0.009 to 0.0105, any two which differed by more than 2 S.E.M. or 0.02 second were considered statistically different (i.e., anterior versus anteroseptal and posterior during the second week).

The number of tracings presenting patterns other than the three mentioned above was too small for any comparison.

DISCUSSION

It is quite apparent that in acute myocardial infarction there is a definite prolongation of the Q-T interval of the electrocardiogram. This prolongation not only varies during the course of the illness but with the electrocardiographic

site of the myocardial injury. It would be foolhardy to postulate that the prolongation of the Q-T interval is dependent on any single physiological, pathological, or physiochemical factor. One might assume, however, that the QT_c characteristically follows some definite pattern and reflects the functional capacity of the ventricular myocardium and its conduction system.

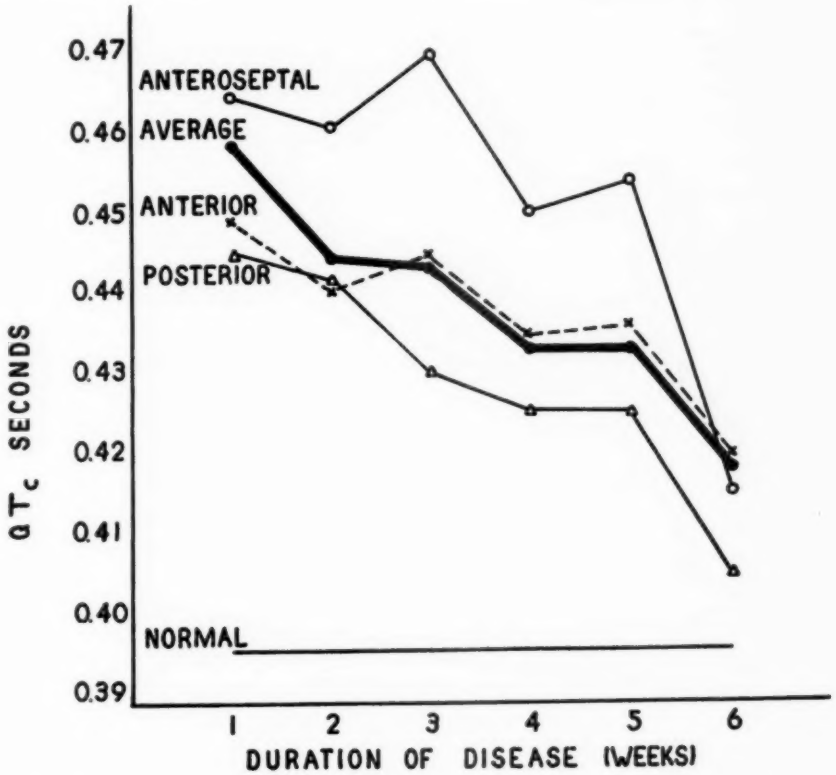

Fig. 2.—Comparison of QT_c values at various stages of the disease process, during the first six weeks of illness. Also demonstrated are the various degrees of prolongation with different localizations of the myocardial damage.

The electrical changes in the heart and their vectoral reflection upon the electrocardiogram occurring with myocardial ischemia and injury have been most thoroughly considered by Bayley.[21] Katz[9] in 1921 and more recently Robb and Turman[14] and Horwitz and Graybiel[15] demonstrated that many simple physiological factors may influence the duration of systole or the Q-T interval. Some of these, such as increased arterial resistance, cellular metabolism, age, sex, and position, may have some influence here.

Cheer,[4] Smily,[5] Berliner,[2] and more recently Taran and Szilagyi[6] found prolongation of QT_c in various pathological cardiac states. Obviously, injury and ischemia of the myocardium materially influence the duration of systole, and the Q-T interval as well as the ST-T segment as described by Bayley.[21]

The role of electrolyte concentration upon systole was noted experimentally by Katz[9] and later by Ashman.[16] Bellet and Dyer,[17] in 1937, first reported prolongation of Q-T intervals in electrocardiograms of persons suffering with diabetic acidosis. A recent clinical study by Nadler, Bellet, and Lanning[18] demonstrated almost a quantitative relationship between the Q-T interval and serum potassium in patients with diabetic acidosis. Simonson and his associates[19] found prolongation of the Q-T interval in the electrocardiograms of human volunteers subjected to semistarvation. The role of electrolyte concentration in myocardial infarction, however, is unknown.

One more factor must be considered in evaluating changes in the duration of the Q-T interval, namely, drugs. Digitalis markedly shortens the Q-T interval. This was demonstrated early by Berliner[2] and confirmed by this investigation. Drugs of the quinine group which prolong ventricular conduction also prolong the Q-T interval. This was shown in a few patients to whom quinidine was administered. QT_c's of 0.5 to 0.57 second were observed, far above what was expected even in acute myocardial infarction.

The complexity of the problem is obvious. However, if the various factors are considered and the effects of drugs eliminated, the duration of the Q-T interval is certainly of value as an aid in confirming the presence of the myocardial ischemia and/or injury in acute myocardial infarction. It may also be considered as some index of the functional capacity of the heart and its conduction system, by virtue of the fact that it varies inversely with the duration of the disease and demonstrates some variations dependent upon the electrocardiographic localization of the myocardial damage.

It is, therefore, suggested that this simple electrocardiographic measurement be made routinely, just as is done with the P-R interval and the duration of the QRS complexes.

SUMMARY

1. The duration of the Q-T interval of the electrocardiogram corrected for the cardiac rate was found to be: (a) 0.397 second in the normal individual; (b) prolonged in acute myocardial infarction (average 0.448 second) and returns toward normal (average 0.411 second) after one month or more; (c) dependent upon the duration of the disease; (d) dependent somewhat upon the electrocardiographic localization of the myocardial damage, and (e) significantly shortened in the presence of digitalis (average 0.386 second).

2. The physiological, pathological, and physiochemical factors affecting the duration of systole or Q-T interval are discussed.

3. It is suggested that the QT_c be made a routine electrocardiographic measurement, but that it not be used synonomously with electrical systole.

The author wishes to thank the various members of the Medical Services of the Jewish Hospital for their permission to review the clinical records of all cases of acute myocardial infaction used in this study, and also express his gratitude to Miss Clara Etzensperger and her record-room staff whose cooperation made this study possible. The kind criticisms and suggestions of Dr. Mitchell Bernstein and Dr. Alexander Margoles are also deeply appreciated.

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THE ELECTROCARDIOGRAPHIC DIAGNOSIS OF CORONARY INSUFFICIENCY BY LEADS DEMONSTRATING THE LEFT VENTRICULAR CAVITY

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THE presence of substernal or precordial pain of short duration but frequent recurrence presents an extremely difficult diagnostic and prognostic problem to the physician. He must decide whether the patient has coronary artery disease or whether the pain is of noncardiac origin, such as cholecystic disease, hiatus hernia, peptic ulcer, or pain of psychic origin. Frequently, the standard electrocardiogram is normal even in proved instances of coronary insufficiency. It is in this type of patient that differentiation is most difficult. The physician has had to resort to making the diagnosis of coronary insufficiency in a negative way by excluding all the other causes; obviously a positive objective diagnosis would be very much more valuable.

Many attempts have been made to demonstrate coronary insufficiency electrocardiographically. Master and his group[1] have devised the standard exercise test. A control electrocardiogram is taken before exercise and after a single or double, standard two-step exercise, tracings from some patients with coronary insufficiency show changes in the S-T segments and T waves. Depressions of S-T greater than 0.5 mm. or changes from upright to isoelectric or inverted T waves are considered a "positive test." Grossman, Weinstein, and Katz[2] also consider the occurrence of premature systoles, and intraventricular or A-V block evidence of a positive test. They report a positive result to exercise tolerance in about 50 per cent of patients with angina pectoris. About two-thirds of patients with coronary symptoms develop pain, dyspnea, weakness or dizziness during the test.

In 1933, Rothschild and Kissin[3] introduced the "anoxemia test" and Levy and his group[4] subsequently investigated it thoroughly. With this test, after a control electrocardiogram, the patient inhales a mixture of 10 per cent oxygen and 90 per cent nitrogen for twenty minutes. If anginal pain is produced, the inhalation is discontinued and an electrocardiogram is taken immediately and at one, five, and ten minutes. If alarming symptoms are produced, 100 per cent oxygen is given for one minute. If no anginal pain is produced, an electrocardiogram is taken at five, ten, fifteen, and twenty minutes after inhalation is stopped. Levy considers a test positive when (1) the arithmetic sum of all the RS-T deviations in Leads I, II, III, and IV_F total 3 mm. or more; (2) when there is partial or complete reversal of the direction of the T wave in Lead I accompanied by RS-T deviation of 1 mm. or more in Lead I; (3) complete reversal of the direction of the T wave in Lead IV_F regardless of RS-T deviation; and (4) partial

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reversal of direction of the T wave in Lead IV_F accompanied by RS-T deviation of 1 mm. or more. This test is considered by many to be too hazardous and cumbersome for routine clinical use. Fatalities have been reported, all patients become cyanotic, and anginal pain, pulmonary edema, faintness, and convulsive seizures may occur.

Several pharmacological methods have been introduced to demonstrate coronary insufficiency. Levine, Ernstene and Jacobson[5] used epinephrine. Several other investigators also tried this method, but it has been completely discarded as being too hazardous. Ergotamine tartrate has also been tried but the dangers attending its use are too great. Stein[6] has used ergonovine and showed changes in the S-T and T wave pattern, similar to the ones produced by anoxemia and exercise. Any unpleasant symptoms were abolished by the use of nitroglycerin.

There are also many other factors which influence S-T and T wave changes. Wendkos[7] demonstrated these changes with increased sympathetic nervous activity in patients with anxiety states and neurocirculatory asthenia. He also showed changes due only to change in position. Many of these changes could be overcome by administration of sympathicolytic drugs. Tachycardia also depresses the S-T segment. This is thought to be due to the increase in the size of the auricular T wave (Ta). Dyspnea, with concomitant hyperventilation, also leads to slight S-T depression and T wave inversion.

In one respect, all these tests which depend on S-T depression and T inversion in the standard limb leads and precordial leads, give only inferential evidence of coronary insufficiency, since they interpret only the epicardial surfaces of the heart.

It is felt that the gradual narrowing of the small arterioles is responsible for the anginal syndrome in a great number of patients. Histologically, the damage produced by the insufficiency of these small vessels is manifested first in the subendocardium since this is the terminal region supplied by the smallest of these vessels. The intracavity pressure also increases the susceptibility of this area to damage. Master[8] and his group have demonstrated histological evidence of narrowed vessels in the subendocardium, chiefly in the left ventricle and particularly at the base of the papillary muscle and in the interventricular septum.

With the introduction of unipolar extremity leads by Wilson, Johnston, McCleod and Barker[9] in 1933 it became possible to demonstrate the right ventricular cavity by the aV_R or V_R leads. This gave the first tracing reflecting a subendocardial area, and the first electrocardiographic evidence of subendocardial damage. Goldberger[10] discusses the elevation of the S-T segment due to true "current of injury" in some patients with coronary insufficiency (Fig. 1).

It was our thought that if we could develop a technique to demonstrate left ventricular cavity, an even greater number of these doubtful cases could be cleared up. This would have the added advantage of simplicity and safety since it would not require compromising the patients' questionable coronary supply with exercise or anoxemia. A lead facing the left ventricular cavity would have the following characteristics: (1) the initial deflection produced by the passage of the impulse from left to right across the septum would be negative since

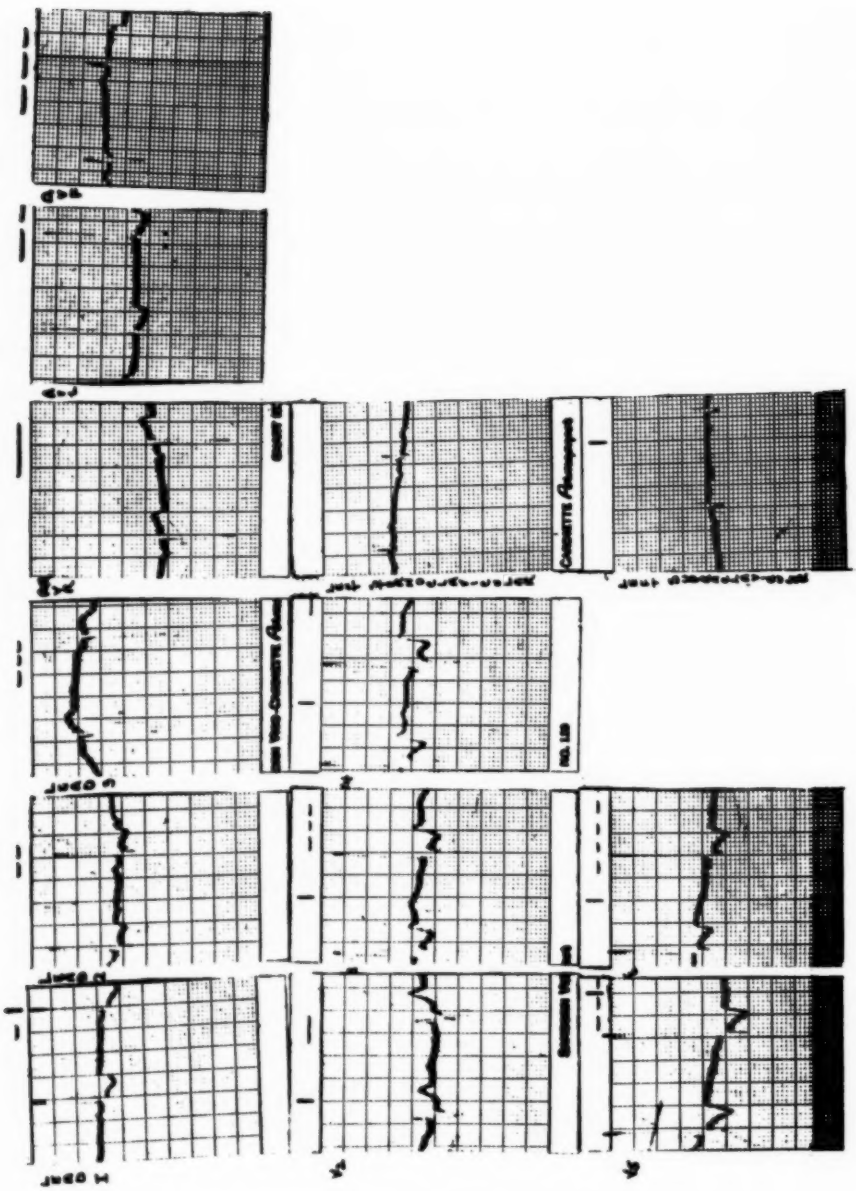

Fig. 1.—Proved instance of coronary insufficiency with marked changes in precordial leads demonstrating the elevated S-T in aV_R.

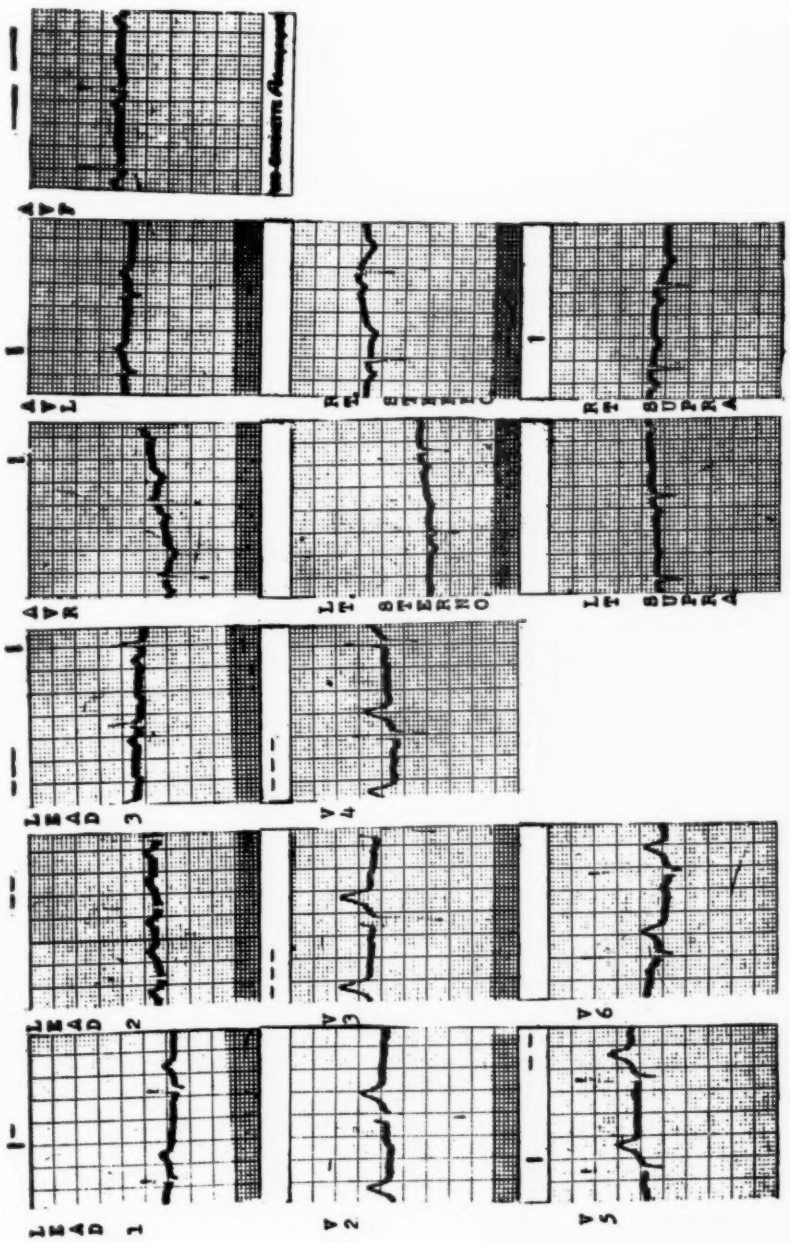

Fig. 2.—Normal electrocardiogram showing the typical QS, inverted T pattern characteristic of left ventricular cavity in left supraclavicular and left sternoclavicular positions.

it is traveling away from the electrode; (2) the deflection produced by the progress of the impulse out through the ventricular musculature would also be negative; and (3) the T wave would normally be inverted, thus producing a QS, inverted T pattern (Fig. 2).

METHOD

We first explored the entire anterior and posterior chest walls in normal individuals taking multiple tracings over this entire area. It became clear after repeated trials that on the anterior chest wall, all leads taken below the level of the second rib would demonstrate either the epicardial surface of the right or left ventricle or the right ventricular cavity. The tracings taken over the posterior chest wall represented either the epicardial surface of the ventricles or "back of the heart," i.e. a QR pattern. However, if the exploring electrodes were placed in the left supraclavicular fossa or over the clavicle at the lateral border of the sternocleidomastoid muscle, a tracing typical of the left ventricular cavity and differing from the tracing of the right ventricular cavity seen in aV_R, could be obtained in a large percentage of patients (Fig. 3.)

Fig. 3.—Showing two sites of placement of electrode: X, sternoclavicular junction; ●, supraclavicular fossa.

RESULTS

One hundred tracings were made, taking the standard limb leads, V_2, V_3, V_4, V_5, V_6, aV_R, aV_L, aV_F and left supraclavicular and left sternoclavicular leads.

In thirty-one tracings, neither the left supraclavicular nor the left sternoclavicular leads demonstrated left ventricular cavity. In these tracings, either

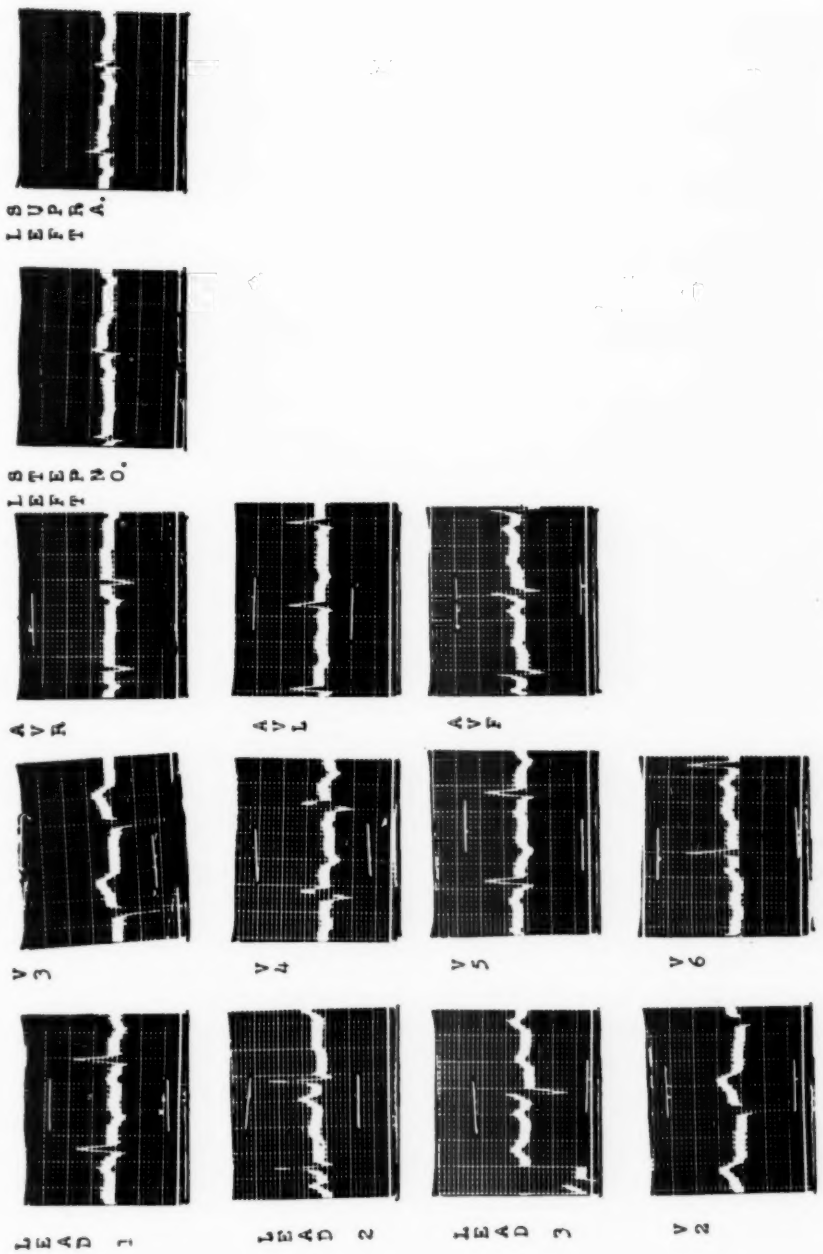

Fig. 4.—Note elevation of S-T segments in "cavity leads" and changes indicative of infarction in standard and precordial leads.

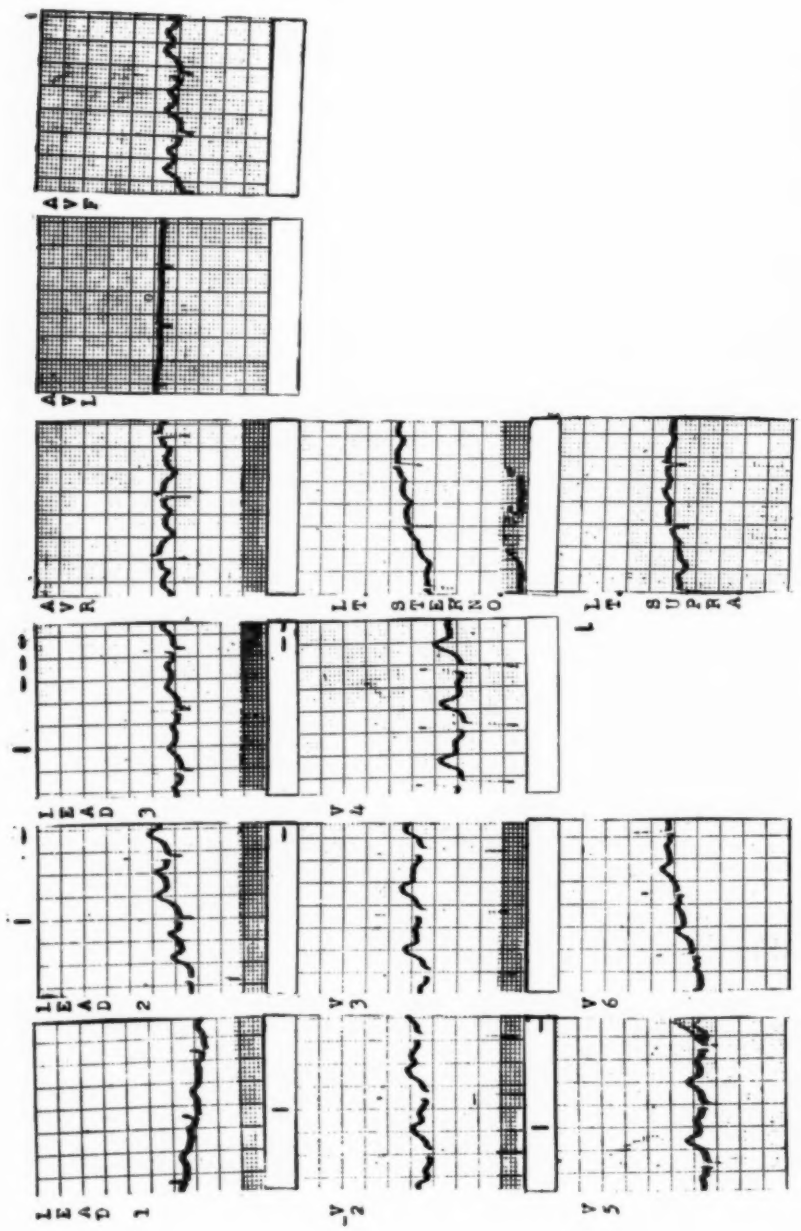

Fig. 5.—Myocardial infarction with changes in precordial leads indicative of epicardial damage, but normal endocardial leads.

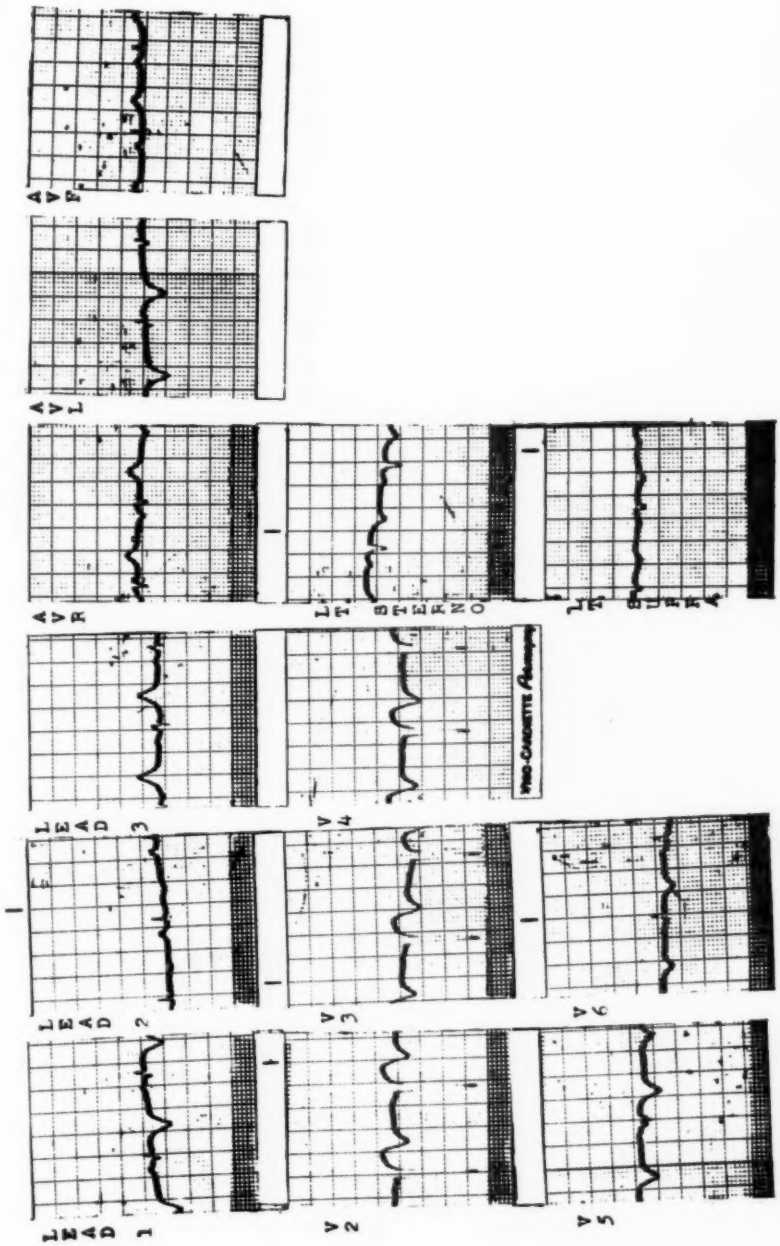

Fig. 6 A.—Note abnormality in right and left ventricular cavity lead as shown by elevated S-T segment in aV_R and left supraclavicular lead—otherwise tracing is normal. The initial R wave in the left sternoclavicular lead indicates that it probably represents epicardial surface of right ventricle.

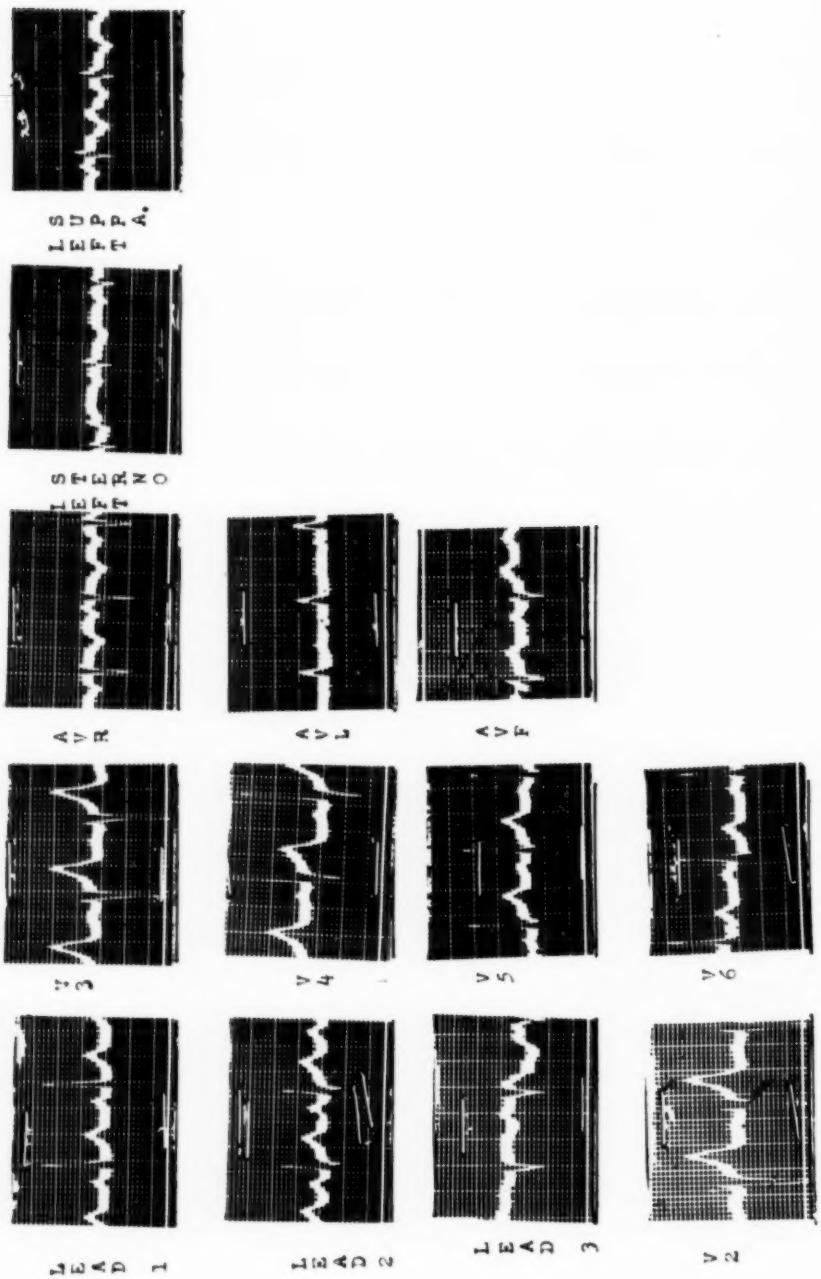

Fig. 6 B.—Note the elevated S-T in left ventricular cavity leads.

right ventricular cavity (similar to aV_R) or epicardial surface of the left ventricle or a QR pattern resembling "back of the heart" was found. Practically all of these tracings showed an intermediate type of heart, i.e. neither vertical nor horizontal; a few were vertical hearts with no rotation. Eight of these patients had angina pectoris, but no definite significant change could be demonstrated electrocardiographically.

In sixty-nine subjects, the left ventricular cavity could be readily demonstrated by this technique. Twenty-nine of these were individuals without cardiac disease or symptoms and on whom control tracings were made. These included hospital personnel and patients with unrelated ailments on whom electrocardiograms were taken. They all showed the typical QS, isoelectric S-T, and inverted T described as normal left ventricular cavity. Of the 100 subjects done, only three patients with a history of angina pectoris had completely normal tracings, i.e., normal standard leads, precordial leads, unipolar extremity leads, and left ventricular cavity leads.

There were twenty-four tracings showing abnormalities, in both the precordial or epicardial surface leads and the supraclavicular and sternoclavicular or left endocardial surface leads. Of these twenty-four, fourteen had angina pectoris and a diagnosis of either coronary insufficiency or myocardial infarction could be made. The remaining ten patients did not exhibit angina but had evidence of coronary arteriosclerosis or left ventricular hypertrophy (Fig. 4).

Five patients showed evidence of abnormality in the precordial (epicardial surface) leads but had normal left ventricular cavity leads. Two of these were patients with acute myocardial infarctions while three had left ventricular hypertrophy (Fig. 5). These latter three did not have subjective angina.

In five patients the standard limb leads, the precordial leads and the unipolar extremity leads were normal but the left ventricular cavity leads showed abnormalities. Four of these had frank angina pectoris; one was a 13-year-old boy with active rheumatic fever. One was a woman, 29 years of age, with subacute bacterial endocarditis, who had no chest pain (Figs. 6A and 6B).

ANALYSIS

Our results readily show that by simple exploration of the chest, we were able to demonstrate electrocardiographically the pattern representative of left ventricular cavity. In 69 per cent of the patients the left supraclavicular fossa or sternocleidomastoid region consistently revealed a QS, inverted T pattern. This percentage increases when one remembers that in a vertically placed heart, the left arm lead will often face the left ventricular cavity and the cavity pattern will be obtained. Thus we have demonstrated a simple technique for exploring the subendocardial surface of the left ventricle. Our primary purpose in this study has been to demonstrate changes indicative of subendocardial damage which one may expect to find in angina pectoris, where standard methods are unsuccessful and without burdening the coronary artery supply to the myocardium by the use of exercise and other similar approaches.

In 5 per cent of the electrocardiograms taken, changes were demonstrated in left ventricular cavity leads, but in none of the other leads. These changes

consisted of either upright T waves, elevation of the S-T segment, appearance of a prominent R wave, or combinations of the latter. All of these patients had clinical evidence of angina pectoris and yet showed no electrocardiographic abnormalities by standard and unipolar limb and precordial leads. These five represent the kind of patients for whom exploration of the left ventricular cavity can be of unequivocal value, by demonstrating changes which are not observed by standard methods. Twenty-four per cent of the tracings taken showed abnormalities of both epicardial and subendocardial surfaces. About half of these subjects had angina pectoris elicited by history. Changes in the standard leads and left ventricular cavity leads could readily be expected in view of the electrocardiographic patterns which were primarily consistent with a diagnosis of acute or subacute myocardial infarct, coronary insufficiency, or left ventricular hypertrophy and strain.

In a further breakdown of these results, 5 per cent of tracings showed abnormal epicardial surfaces but the left ventricular cavity leads showed no abnormalities whatsoever. Three of these patients had evidence, electrocardiographically, of left ventricular hypertrophy while the other two had acute myocardial infarction. In view of abnormal epicardial surface and normal subendocardium, one may postulate that the damage did not extend into the subendocardium in these patients with acute infarction.

Many attempts have been made to prognosticate the outcome of myocardial infarction from the electrocardiogram. Results are somewhat inconsistent. Recently Mills and his associates[11] showed that persistence of S-T segment elevation increased the severity of the prognosis. Other investigators point out that persistence of S-T segment elevation indicates ventricular aneurysm. The location of the infarction, whether it be in the anterior or posterior wall, does not seem to affect the prognosis. The extent of the damage can also be determined by exploration of the chest with the precordial electrode. The amount of epicardial damage can be approximated by this exploration but it does not tell one the depth of involvement. It seems rational to draw the conclusion that a lesion involving both epicardium and subendocardium will increase the gravity of the prognosis over a lesion involving only the epicardial surface of the left ventricle. In addition, without endocardial and subendocardial damage, the likelihood of mural thrombi forming is decreased and the possibility of thromboembolic complications becomes less.

DISCUSSION

It is apparent that this method does not in itself answer completely the diagnostic difficulties associated with angina pectoris. However, it shows subendocardial damage directly in a manner which can not be confused with ventricular hypertrophy and certain other functional causes of T wave changes, such as tachycardia, sympathetic effects, potassium effects, etc. This method has the tremendous advantage of safety and simplicity, it does not embarrass the patients' damaged myocardium and it can be applied without additional time, trouble, or expense. In a patient already distressed with acute chest pain, it is obvious that no procedure which requires exertion or anoxemia can be performed.

We also feel that this method can be used, in conjunction with the other usual methods which put a strain on the myocardium, when doubt exists even after electrocardiograms including these left ventricular cavity leads have been taken. We feel that elevation of the S-T segment will occur with greater frequency and more specific accuracy than in the conventional leads and we are continuing work along these lines.

SUMMARY AND CONCLUSIONS

1. Coronary insufficiency is produced by relative anoxemia of the myocardium.

2. The damage is usually greatest in the subendocardial areas of the left ventricle.

3. It is sometimes impossible to make an electrocardiographic diagnosis of coronary insufficiency by standard limb leads, precordial leads and unipolar extremity leads, because these interpret mainly the epicardial portions of the heart.

4. Electrocardiographic leads demonstrating the left ventricular cavity would give specific objective evidence of coronary insufficiency.

5. We have demonstrated a simple method, not previously described, which shows this area in a large percentage of cases.

6. This method does not compromise an already damaged coronary circulation.

7. The method can be used in conjunction with other "strain" methods.

8. These leads may have prognostic value for patients with myocardial infarction by demonstrating whether the damage has progressed through and through from the epicardium to the endocardium.

We wish to acknowledge our appreciation to Dr. Leo H. Criep, Director of the Electrocardiographic Laboratory, for his kind cooperation and to Mrs. Evelyn Patton for her valuable technical assistance.

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THE ELECTROCARDIOGRAPHIC SIGNS OF MYOCARDIAL INFARCTION IN THE PRESENCE OF BUNDLE BRANCH BLOCK

II. Myocardial Infarction With Right Bundle Branch Block

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THE diagnostic electrocardiographic signs of myocardial infarction superimposed on bundle branch block were studied in the experimental animal by Rosenbaum and associates.[1] In a previous report we analyzed the features of myocardial infarction in the presence of left bundle branch block in clinical cases.[2] The present study was made on a large series of clinical cases in an attempt to determine the signs of myocardial infarction superimposed on right bundle branch block.

Ninety-two patients with right bundle branch block were studied. In sixty patients the diagnosis of myocardial infarction was made; it was based on: (1) post-mortem findings in twelve, (2) evidence of infarction shown by electrocardiograms which were obtained either prior to the development of right bundle branch block or after its disappearance, (3) electrocardiographic changes similar to those occurring in the experimental animal after production of right bundle branch block and myocardial infarction,[1] (4) progressive electrocardiographic changes such as are observed in serial records in the presence of acute myocardial infarction, and (5) clinical and laboratory findings supporting the diagnosis of myocardial infarction.

Thirty-two patients presented what appeared to be "pure" right bundle branch block.* The difficulty of finding a sufficiently large test group presenting "uncomplicated" bundle branch block has been pointed out in the past.[2] It was necessary to eliminate not only patients who presented a history suggestive of myocardial infarction, but also those who at any time had complained of angina of effort; for myocardial infarction sometimes manifests itself only by uncharacteristic short spells of angina pectoris. Because of these limitations in the classification of patients with "pure" bundle branch block, only a small group was available for this study. The difficulty of evaluating such a small series for statistical purposes is obvious.

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*The terms "pure" or "uncomplicated" bundle branch block are used in the sense that there was neither a suggestive history nor any other evidence of myocardial infarction. We realize that, in the majority of patients, bundle branch block is due to coronary arteriosclerosis and is the result of an ischemic lesion interrupting the continuity of the conduction fibers.

ELECTROCARDIOGRAPHIC FEATURES OF UNCOMPLICATED RIGHT BUNDLE BRANCH BLOCK

The features of the QRS complex that are characteristic of right bundle branch block in the canine electrocardiogram and in man were described by Rosenbaum and associates[1] and by Wilson.[3] In human tracings (Fig. 1) the QRS deflection, as a rule, has a duration of 0.12 second or more. In leads from the right side of the precordium, the QRS complex is usually bifid and either entirely upright or has a small initial upstroke which is separated by an S wave from a late, broad, slurred upward deflection; a Q wave is only exceptionally present. In leads from the left side of the precordium, a slender R wave that may or may not be preceded by a Q wave is followed by a broad, slurred S wave of variable amplitude. When the duration of the QRS deflection is 0.12 second or more, the finding of an S deflection in Lead I is nearly always characteristic of right bundle branch block; a Q wave may or may not be present in Lead I.

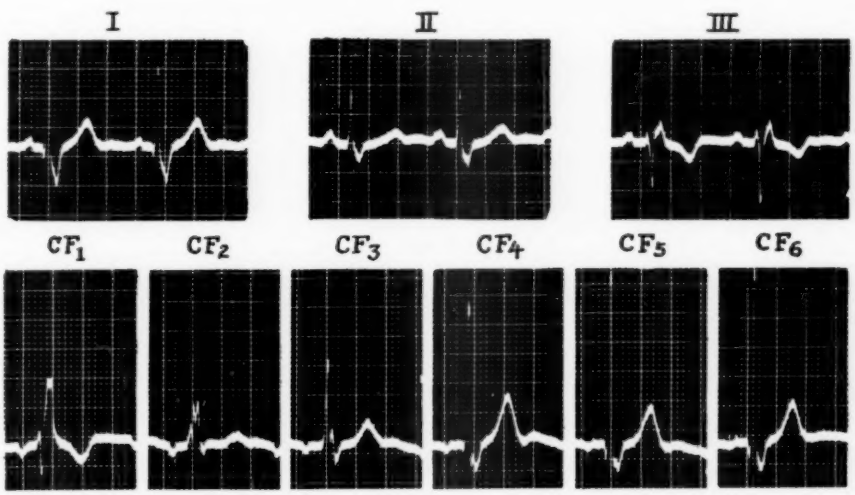

Fig. 1.—Electrocardiogram of a 68-year-old woman who gave no history of anginal pain or anything to suggest a myocardial infarction. The QRS is 0.12 second wide. In Lead I, the finding of a broad, slurred S wave in addition to a small Q wave and slender R deflection is suggestive of right bundle branch block. In Lead III, QRS is M-shaped and the T wave is inverted. The chest leads CF_4 through CF_6 are similar to Lead I. The right-side precordial pattern, as presented in Lead CF_1, shows an M-shaped QRS complex which consists of a small R, a deep S wave, and a late R; the intrinsic deflection occurs about 0.1 second after the onset of the QRS complex. These are the features of uncomplicated right bundle branch block. Note that the T waves are upright in Lead I and in the leads showing the left side precordial pattern, and are inverted in Leads III and CF_1.

Rosenbaum and associates employed unipolar precorial leads. For our patients with uncomplicated right bundle branch block, CR leads were used in nineteen instances, CF leads in eleven, V leads in one, and both CR leads and V leads in another instance. The shape of the electrocardiogram was essentially the same irrespective of the kind of chest leads employed. For twenty-three of the patients, six precordial leads were available; for six patients, five precordial leads

were taken; and for two patients, four precordial leads were taken. In one, only three precordial leads were available which, however, presented the characteristic right and left side precordial patterns of right bundle branch block.

Table I shows, in thirty-two patients with uncomplicated right bundle branch block, the incidence of Q waves, the maximum measurements for the amplitude of Q, and the frequency of those Q waves measuring more than one-quarter of the amplitude of the R wave in the same lead. Q waves were often present in the limb leads and in the chest leads from C_4 through C_6;* they were observed only once in leads from C_1 and C_2, and twice in C_3. To differentiate Q waves that are part of the right bundle branch block pattern from those due to myocardial infarction, measurement of the exact amplitude of Q is less helpful than is the ratio of amplitude Q/R in the same lead. In uncomplicated right bundle branch block, this raio was invariably less than one-fourth in Lead I and in the chest leads. It was greater than one-fourth in six patients in Lead III and in a single patient in Lead II; in the latter, the amplitude of Q_2 was one-third the amplitude of R_2. In Lead III a Q wave was present in thirteen subjects. In six instances, the amplitude of Q_3 measured from one-third to double the amplitude of R_3. As a rule, the duration of the Q wave was less than 0.04 second. In two instances, Q_3 measured more than 0.04 second, and was also conspicuously slurred and notched. This was not observed in other Q waves in Lead III or in any of the other leads. QS deflections were never present.

TABLE I. Q WAVES IN THIRTY-TWO PATIENTS WITH UNCOMPLICATED RIGHT BUNDLE BRANCH BLOCK

LEAD:	I	II	III	C_1	C_2	C_3	C_4	C_5	C_6
Q waves present in:*	18	15	13	1	1	2	10	14	14
Maximum amplitude of Q (mm.):	2.8	1.3	8.5	1.2	1.2	0.7	1.9	4.8	5.5
Q waves measuring more than one-fourth amplitude of R in the same lead:*	0	1	6	0	0	0	0	0	0

*The figures refer to the number of patients.

The incidence of low R deflections in uncomplicated right bundle branch block is of interest because significant downward deflections of the QRS complex are sometimes preceded by small upstrokes in the presence of myocardial infarction. Table II shows the incidence of R waves with an amplitude of 2 mm. or less and the minimum values for the amplitudes of R waves in thirty-two patients with uncomplicated right bundle branch block. Amplitudes of 2 mm. or less were never observed in Leads C_4 through C_6; they were present once in Lead C_3, twice in Lead I, and three times in Leads II and C_2. Low R waves were most frequently observed in Leads III and C_1. The ratio of amplitudes S/R in leads with low R deflections may be helpful in the differentiation of "normal" RS

*For the sake of brevity and because the site of the indifferent electrode varied in different patients, chest leads will be described by the letter C with affixed figures to indicate the position of the exploring electrode.

deflections from significant RS complexes, which occasionally accompany myocardial infarction and are referred to as Q-wave equivalents. The maximum values for the ratio S/R in patients with uncomplicated right bundle branch block are given in Table II (third row). The evaluation of these measurements for the differentiation of Q-wave equivalents will be discussed later.

TABLE II. LOW R DEFLECTIONS IN THIRTY-TWO PATIENTS WITH UNCOMPLICATED RIGHT BUNDLE BRANCH BLOCK

LEAD:	I	II	III	C_1	C_2	C_3	C_4	C_5	C_6
Incidence of R waves with amplitudes of 2 mm. or less:*	2	3	14	11	3	1	0	0	0
Minimum values for the amplitude of R (mm.):	1.8	0.9	0.2	0.6	0.6	1.0	4.0	4.9	5.0
Maximum ratio of amplitude S/R in leads with R waves 2 mm. high or less:	3.3	9	30	8	11	9	—	—	—

*The figures refer to the number of patients.

A QRS pattern characterized by low voltage in Lead I, and S waves in Leads II and III of much larger amplitude than R_1 (pattern $r_1 S_2 S_3$) was not observed with uncomplicated right bundle branch block. There was only one electrocardiogram which presented features approaching that pattern, but the amplitude of R_1 was 6.2 millimeters. In one tracing taken in uncomplicated right bundle branch block a QRS pattern was present in which the major deflection was directed downward in all limb leads.

TABLE III. INCIDENCE OF DOWNWARD DIRECTED, WIDE, AND THICKENED QRS DEFLECTIONS, AND THEIR RELATIONSHIP TO POSITION OF THE RS-T SEGMENTS AND DIRECTION OF T WAVES IN THIRTY-TWO* PATIENTS WITH UNCOMPLICATED RIGHT BUNDLE BRANCH BLOCK

LEAD:	I	II	III	C_1	C_2	C_3	C_4	C_5	C_6
Downward directed, wide, and thickened QRS deflections present:†	32	23	1	0	6	16	23	31	22
Downward directed, wide, and thickened QRS deflections with upright T waves:†	32	22	0	0	5	14	22	30	22
Downward directed, wide, and thickened QRS deflections with elevated RS-T junctions:†	22	17	1	0	6	15	17	23	17
Downward directed, wide, and thickened QRS deflections with isoelectric RS-T junctions:†	9	3	0	0	0	0	5	6	3
Downward directed, wide, and thickened QRS deflections with depressed RS-T junctions:†	1	3	0	0	0	1	1	2	2

*Six precordial leads were not available in every instance. C_1 was absent in one; C_3 in two; C_4 in one; C_6 in nine patients.

†The figures refer to the number of patients.

In right bundle branch block the deviation of the RS-T segment and the direction of the T wave tend to be opposite to that QRS deflection which is prominent by prolonged duration, slurring, or notching rather than by large amplitude. Table III indicates the incidence of downward directed, wide, and thickened QRS deflections; the latter were most frequent in Leads I and II and in precordial leads from left-side positions. They were almost invariably associated with upright T waves, and the RS-T junction was elevated in the majority of the tracings. Table IV shows the incidence of upright, wide, and thickened QRS deflections; the latter predominated in Leads III, C_1, and C_2. They were most often associated with inverted or semi-inverted ($\mp$) T waves. Slight elevation or isoelectric position of the RS-T junction was encountered almost as frequently as depression of the RS-T junction.

TABLE IV. INCIDENCE OF UPRIGHT, WIDE, AND THICKENED QRS DEFLECTIONS AND THEIR RELATIONSHIP TO POSITION OF THE RS-T SEGMENTS AND DIRECTION OF T WAVES IN THIRTY-TWO* PATIENTS WITH UNCOMPLICATED RIGHT BUNDLE BRANCH BLOCK

LEAD:	I	II	III	C_1	C_2	C_3	C_4	C_5	C_6
Upright, wide, and thickened QRS deflections present:†	0	1	26	31	23	6	0	1	0
Upright, wide, and thickened QRS deflections with inverted or minus-plus T waves:†	0	1	21	28	13	6	0	0	0
Upright, wide, and thickened QRS deflections with depressed RS-T junctions:†	0	0	7	16	10	5	0	0	0
Upright, wide, and thickened QRS deflections with isoelectric RS-T junctions:†	0	0	10	10	5	1	0	0	0
Upright, wide, and thickened QRS deflections with elevated RS-T junctions:†	0	1	9	5	8	0	0	1	0

*Six chest leads were not available in every patient. C_1 was absent in one; C_2 in two; C_4 in one; C_6 in nine patients.

†The figures refer to the number of patients.

Table V shows the direction of the T wave and the position of the RS-T junction in uncomplicated right bundle branch block. Upright T waves predominated in Leads I and II, and in the precordial leads C_3 through C_6; in Leads I and C_6, the T waves were invariably upright. In Lead C_5, upright T waves were present in all but one tracing, which showed a diphasic ($\mp$) T wave. In Lead I and in the precordial leads C_4 through C_6, the amplitude of the T wave was never less than 1.0 millimeter. In Lead II, where the T wave was upright in twenty-seven instances, the amplitude of T was 1.0 mm. or more in twenty-four, and 0.8 mm. in three instances. In Lead III the T wave was upright in six tracings; its amplitude ranged from 0.5 to 1.8 millimeters. Upright T waves were associated, as a rule, with elevated or isoelectric RS-T junctions. Depression of the RS-T junction with upright T waves was observed once in Lead I, and in the chest leads C_1, C_3, C_4, C_5, and C_6, respectively; the depression was

usually slight, ranging from 0.1 to 0.6 millimeter. In only one instance, in Lead C_4, the depression of the RS-T segment, in association with an upright T wave, measured 1.4 millimeters.

TABLE V. DIRECTION OF T WAVES AND POSITION OF THE RS-T SEGMENTS IN THIRTY-TWO* PATIENTS WITH UNCOMPLICATED RIGHT BUNDLE BRANCH BLOCK

LEAD:	I	II	III	C_1	C_2	C_3	C_4	C_5	C_6
Upright T waves:†	32	27	6	3	17	23	26	31	23
Isoelectric T waves:†	0	0	2	0	0	0	0	0	0
Inverted or minus-plus T waves:†	0	5	24	28	15	8	5	1	0
RS-T junction elevated:†	22	22	13	5	16	20	19	24	18
RS-T junction isoelectric:†	9	5	10	10	5	3	7	6	3
RS-T junction depressed:†	1	5	9	16	11	7	5	2	2

*All six chest leads were not available in every patient. C_1 was absent in one; C_3 in two; C_4 in one; C_6 in nine patients.

†The figures refer to the number of patients.

Inverted or semi-inverted (∓) T waves (Table V) were often seen in Leads III, C_1, and C_2; they were never observed in Leads I or C_6, and were present in Lead C_5 in only one tracing. Simultaneous inversion of T_2 and T_3 was observed in one patient. Inverted T waves with symmetrical limbs, resembling the V-shaped T waves of myocardial infarction, occurred in uncomplicated right bundle branch block in fourteen subjects in Lead III; in one, in Lead II; and in three instances in Lead C_3. Inverted or semi-inverted (∓) T waves were most often associated with depressed RS-T junctions; in sixteen instances the RS-T junctions were isoelectric and in fourteen instances elevated; the latter was most frequent in Lead III. The maximum elevation of the RS-T junction, when the T wave was inverted, measured 0.7 millimeter.

TABLE VI. MAXIMUM MEASUREMENTS OF THE AMPLITUDE OF INVERTED T WAVES AND OF ELEVATION AND DEPRESSION OF THE RS-T JUNCTION IN THIRTY-TWO PATIENTS WITH UNCOMPLICATED RIGHT BUNDLE BRANCH BLOCK

LEAD:	I	II	III	C_1	C_2	C_3	C_4	C_5	C_6
Maximum amplitude of inverted T waves (mm.):	0	1.5	3.1	6.8	8.0	6.0	0	0	0
Maximum elevation of the RS-T junction (mm.):	1.0	0.9	0.6	0.5	4.0	3.0	1.8	2.5	1.2
Maximum depression of the RS-T junction (mm.):	0.4	0.8	1.0	1.3	1.7	1.5	1.4	0.8	0.6

Table VI gives the maximum measurements for the amplitude of inverted T waves, and for the deviations of the RS-T junction in limb and chest leads in thirty-two patients with uncomplicated right bundle branch block. In Leads II and III, the amplitude of inverted T waves was usually less than 3.0 mm., in one instance, in Lead III, it measured 3.1 millimeters. Much deeper T waves were observed in the precordial leads C_1 through C_3, the maximum values ranging from 6.8 to 8.0 millimeters.

Elevation of the RS-T junction (Table VI) in the limb leads was usually less than 1.0 mm.; in a single instance, an elevation as high as 1.0 mm. was observed in Lead I. In the chest leads elevations above 1.0 mm. were frequently present; in three instances there was an elevation of more than 2.0 mm.; the greatest elevation, 4.0 mm., was observed once in Lead C_2. It has been mentioned that elevation of the RS-T junction measuring up to 0.7 mm. was quite often associated with inversion of the T wave. When the RS-T junction was elevated 1.0 mm. or more, the T wave was invariably upright, and the summit of T was at least as high (and in most cases, much higher) above the level of the RS-T junction as the latter was above the level of reference (onset of the QRS complex).

Depression of the RS-T junction (Table V) was most frequent in Lead III and in the leads from the right side of the precordium. It was present only once in Lead I, and twice in Leads C_5 and C_6. In the limb leads, depression of the RS-T junction did not exceed 1.0 mm. (Table VI). In the chest leads, it was, in a few instances, greater than 1.0 mm.; the maximum depression was 1.7 mm. and was observed in Lead C_2 in one subject.

When the T wave was upright, the RS-T segment (first limb of T) usually showed a downward bow. In exceptional cases the first limb of the T wave followed a straight course; this happened in the transitional zone (Leads C_3, C_4, or C_5) between those precordial leads presenting a typical right-side pattern and the leads showing a characteristic left-side pattern. The transitional zone most often exhibited deviations from the pattern prevailing in the other leads. In four instances, notched T waves were observed (in Leads C_2 or C_3); in three instances upward convex RS-T segments were seen, followed by minus-plus T waves (in the Leads C_2 through C_4).

Diphasic T waves of the plus-minus type or "coronary T waves" were not observed in uncomplicated right bundle branch block. A dome-shaped T wave was present in Lead II in one tracing. The T wave in Lead I, which was invariably upright, was higher than T_3 except in one subject; this patient had a small heart in vertical position.

ANTERIOR INFARCTION WITH RIGHT BUNDLE BRANCH BLOCK

Our study includes twenty-five patients with right bundle branch block for whom the diagnosis of anterior infarction was made. In four, the diagnosis was confirmed by post-mortem examination. In one, myocardial infarction was indicated by changes in tracings obtained prior to the development of right bundle branch block. In eight, serial records showed progressive changes such as accompany recent anterior infarction. In the remaining twelve, the diagnosis was based on clinical and laboratory evidence and on electrocardiographic signs that have been observed in experimentally produced infarction in the presence of preexisting right bundle branch block.

CASE 1.—R. E. was a 62-year-old man. In the autumn of 1943 he had repeated attacks of anginal pain during a period of ten days. The last and severest attack started on November 6 and had not yet ceased when the patient was admitted to the hospital on Nov. 7, 1943.

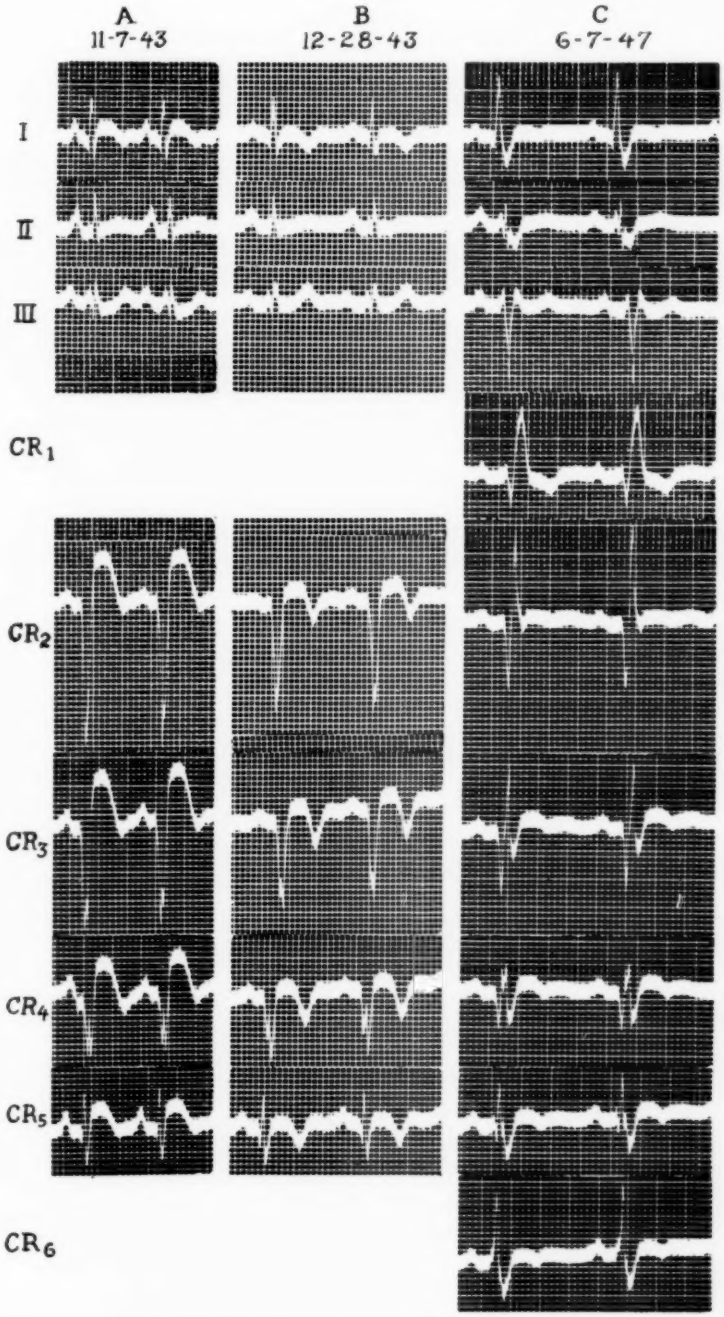

Fig. 2.—Case 1. *A*, electrocardiogram made on the day of the coronary attack. QRS is of normal duration. There are signs of acute anterior infarction. *B*, seven weeks after *A*. Healing stage of anterior infarction. *C*, three and one-half years after *A*. Right bundle branch block has developed. In addition, there are signs of anterior infarction. In Leads CR_2 through CR_4 significant Q waves precede late R deflections. T_1 is inverted. In Leads CR_3 through CR_5, the RS-T junction is significantly elevated and the T wave is inverted.

The first electrocardiogram taken on Nov. 11, 1943, (Fig. 2,*A*) shows QRS complexes of normal duration and signs of recent anterior infarction. The second tracing (*B*) taken Dec. 12, 1943, exhibits more advanced changes corresponding to the healing stage of anterior infarction. An electrocardiogram, taken three and one-half years later (Fig. 2, *C*), shows that right bundle branch block has developed. In addition, there are signs of anterior infarction similar to those in the previous tracings. T_1 is inverted. Lead CR_1 shows no changes other than those due to right bundle branch block. In Leads CR_2 through CR_4, significant Q waves precede late R deflections. Leads CR_3 through CR_6 show significant elevation of the RS-T junction and inversion of the T wave.

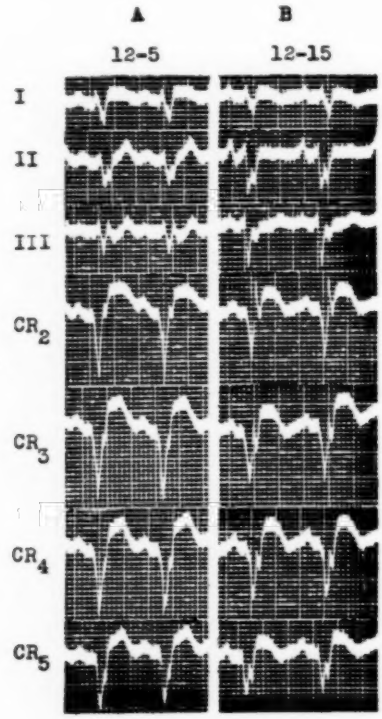

Fig. 3.—Case 2. *A*, **electrocardiogram made one day after the coronary attack. The duration of the QRS complex is 0.13 second. The finding of an S wave in Lead I suggests right bundle branch block. In the limb leads the major QRS deflection is directed downward and of low voltage. In Lead I, there is a small Q wave and the RS-T junction is significantly elevated. Extensive anterior infarction is indicated in the chest leads by QS deflections which are associated with marked elevation of the RS-T segment. A notch in the ascending limb of the QS deflections marks the position of the late R waves.** *B*, **eleven days after the attack. Marked elevation of the RS-T segment persists in the chest leads. The late R deflections are more distinctly developed in the leads from the right side of the precordium.**

The patient died on July 29, 1947. Post-mortem examination revealed an old myocardial infarction which occupied the anterior third of the interventricular septum and the anterior wall of the left ventricle from base to apex. The infarction extended to the lateral wall, involving about half of the circumference of the left ventricle.

Summary: Signs of anterior infarction were present in electrocardiograms taken prior to the development of bundle branch block. After right bundle branch block had developed, similar signs of infarction persisted. In the chest leads there were significant Q waves, which preceded late R deflections; in Lead I and in the chest leads inversion of the T wave was associated with significant elevation of the RS-T segment. Post-mortem examination revealed an old extensive

infarction which involved part of the septum and most of the anterior and lateral walls of the left ventricle.

CASE 2.—T. E. was a 56-year-old policeman. On Dec. 4, 1945, after struggling with a drunkard, he experienced excruciating substernal pain which radiated to the left arm and lasted for several hours. Death occurred suddenly on Dec. 17, 1945.

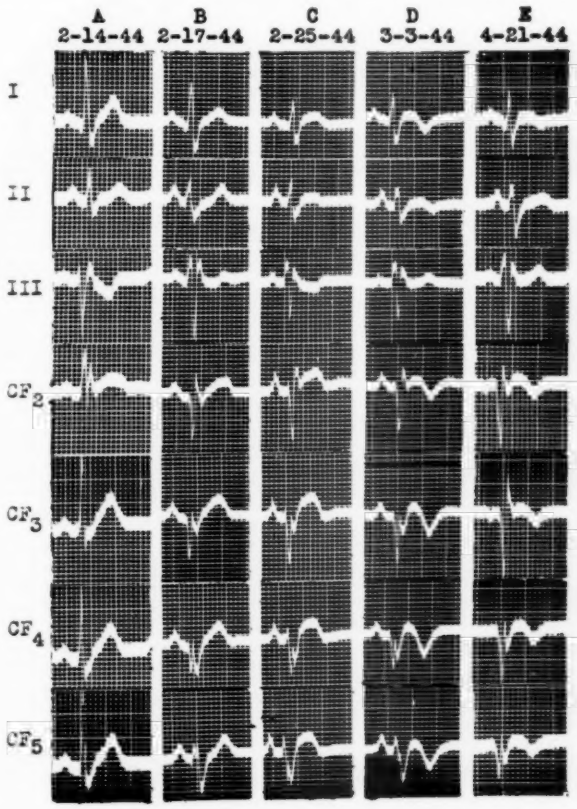

Fig. 4.—Case 3. *A*, electrocardiogram made before the major attack of chest pain. The pattern of right bundle branch block is present. *B*, on the day of the coronary attack. In Lead I, Q has become wider and the R deflection lower. Significant Q waves have appeared in Leads CF_2 through CF_4. The R wave is abnormally low in Lead CF_5. The T waves are rounded in Leads CF_2 and CF_3. The changes indicate anterior infarction. *C*, eight days after the attack. Lead I and the chest leads, show significant elevation of the RS-T junction and a terminal dip of the T wave. In Leads CF_2 through CF_4, the deep downward deflection of QRS is preceded by a small upstroke. *D*, two weeks after the attack. In Leads CF_2 through CF_4, tiny upstrokes are still noted in front of the significant negative QRS deflections (Q-wave equivalents). The T wave is inverted in Leads I, II, and in the chest leads. *E*, two months after the attack. Significant Q waves are present in all chest leads. The changes of the T waves are regressive.

The first electrocardiogram (Fig. 3,*A*) was taken one day after the attack. The duration of the QRS deflection is 0.13 second. In the limb leads, the QRS complex is slurred, notched, and of low voltage; the major QRS deflection is directed downward. The finding of an S deflection, in addition to small Q and R waves, in Lead I suggests right bundle branch block. The small Q_1 is probably significant because it is associated with a low R wave. Lead I shows, in addition, significant elevation of the RS-T segment and a terminal dip of the T waves. In the chest leads, extensive anterior infarction is indicated by QS deflections and abnormal elevation of the RS-T segment. A notch in the ascending limb of the QS deflections indicates the position of the late R deflections.

In the second tracing (Fig. 3,*B*) which was taken eleven days after the attack, marked elevation of the RS-T segment persists. In the precordial leads from the right side, the R deflections, which mark the delayed activity of the right ventricle, are more prominent.

Post-mortem examination revealed recent myocardial infarction with an aneurysmal bulge the size of a grapefruit which involved the apical region, the lower part of the interventricular septum, and the lateral wall of the left ventricle.

Summary: In the presence of right bundle branch block, extensive anterior infarction (confirmed by post-mortem examination) was indicated in the chest leads by QS deflections and significant elevation of the RS-T segment; in Lead I by a small but significant Q wave and abnormal elevation of the RS-T segment. The limb leads showed a QRS pattern consisting of downward-directed major deflections of low voltage.

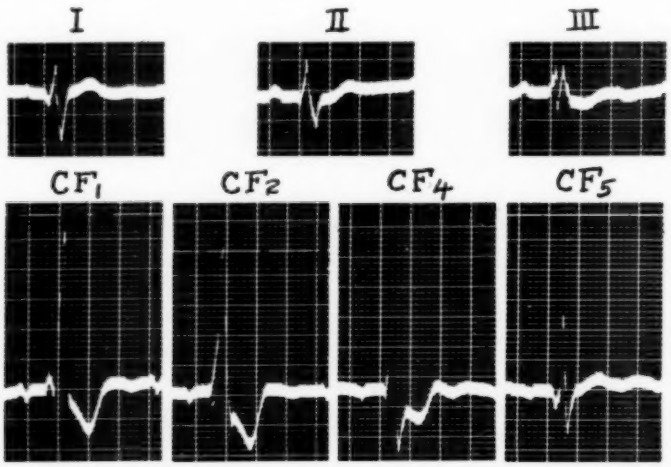

Fig. 5.—Case 4. Electrocardiogram made six years after an attack of chest pain which was suggestive of cardiac infarction. The tracing shows the pattern of right bundle branch block and signs suggestive of digitalis effect (in Leads II, III, CF_2, and CF_4). The wide, slurred Q wave in Leads I and CF_5 may represent the residual effects of an old anterolateral infarction.

Case 3.—E. U., a 51-year-old physician, had complained of mild effort angina for five years. An electrocardiogram taken at the onset of his illness had shown right bundle branch block. During the first half of February, 1944, the patient suffered short attacks of anginal pain when he rested. On Feb. 17, 1944, he experienced crushing chest pain associated with cold perspiration. This attack was followed by low-grade fever, leucocytosis, and fall of the blood pressure; a pericardial friction rub was heard.

The first electrocardiogram (Fig. 4, *A*) was taken three days prior to the major attack of chest pain. It shows the pattern of right bundle branch block. Tracing *B* was obtained on the day of the attack. In Leads CF_2 through CF_4, the initial upstroke is replaced by a significant Q wave. In Lead CF_5, the R deflection is abnormally low. In Lead I, a Q wave which was previously present has become wider, and the amplitude of R and T waves has diminished. In Leads CF_2 and CF_3, the T waves are rounded. The changes are indicative of anterior infarction. Tracing *C* was taken eight days after the attack. It shows in Lead I and in the chest leads significant elevation of the RS-T junction and a slight terminal dip of the T wave. The deep Q wave that was present in Leads CF_2 through CF_4, in the previous tracing, is now preceded by a small upstroke, which measures less than 1.5 millimeters. Tracing *D*, taken two weeks after the attack, shows inversion of the T wave in Leads I, II, and in the chest leads. In Leads CF_2 through CF_4, the significant downstroke of the QRS complex is preceded by a tiny upstroke (Q-wave equivalent). Tracing *E* was obtained two months after the attack. Deep Q waves are present in all chest leads; the changes of the T wave are regressive.

Summary: Right bundle branch block was present prior to the attack of chest pain. Serial tracings which were obtained subsequently, demonstrated the development of significant, progressive changes, indicative of anterior infarction. Significant Q waves in the chest leads were temporarily replaced by Q-wave equivalents.

CASE 4.—W. R., a 57-year-old man, had an attack of terrific pain in the precordial region and left arm in 1939. The pain was not influenced by nitroglycerin; it was relieved after lasting for one hour by the hypodermic injection of morphine. Five years later, dyspnea and signs of congestive heart failure developed. Because of these complaints the patient was hospitalized in 1944 and 1945.

An electrocardiogram (Fig. 5) was taken on Sept. 18, 1945. It shows the pattern of right bundle branch block. An unusually wide and slurred Q wave is present in Leads I and CF_5. This may be the residuum of an old (anterolateral) infarction, which is strongly suggested by the history of a severe and prolonged anginal pain. The marked depression of the RS-T junction in Leads II and III, and nearly complete inversion of the T wave in Leads CF_2 and CF_4 are probably in part due to the effect of digitalis.

Summary: The history of the patient suggested cardiac infarction that occurred six years prior to the examination. The electrocardiogram showed, in addition to right bundle branch block, wide, slurred Q waves in Leads I and CF_5, which were interpreted as residua of an old anterolateral infarction.

CASE 5.—D. R., a 60-year-old woman, had been known to have hypertension for several years. A few days prior to admission to the hospital she suddenly experienced pain in the precordial region and in the left arm, and felt very weak. The next day the chest pain recurred and lasted even longer than previously. The patient was hospitalized on June 8, 1944. Her blood pressure, on that day, was 200/130; it dropped to 138/82 two days later. Leucocytosis, slight elevation of temperature, and increase in the sedimentation rate followed.

The first electrocardiogram (Fig. 6,*A*) was taken on June 8, 1944. It shows, in addition to right bundle branch block, some features that are suggestive of anterior infarction. The amplitude of Q_1 is about one-fourth that of R_1. T_1 is inverted and T_3 is unusually high (3 mm.). In Leads CR_2 and CR_3, which present the left-side pattern, the T waves are inverted. In Leads CR_4 and CR_5, the T waves are diphasic and low. Tracing *B*, which was taken about one year after *A* (June 27, 1945), shows regressive changes. In Lead I the size of the R wave has increased so that the Q wave now measures less than one-eighth of the amplitude of the R wave. T_1 has turned upright but is lower than T_3. In Leads CR_2 and CR_3, the T wave is diphasic; in the leads from the left side of the precordium, T is upright and higher than previously.

Summary: Clinical and laboratory findings suggested an acute cardiac infarction. The electrocardiogram showed the pattern of right bundle branch block. Infarction of the anterior wall was indicated by inverted T waves in Lead I and by unusually high T waves in Lead III; also by diphasic or inverted T waves in the precordial leads presenting the left-side pattern. The changes had regressed one year later.

CASE 6.—M. E. was a 70-year-old man. On July 7, 1944, he experienced repeated attacks of crushing chest pain with radiation to both arms; each attack lasted for a few minutes. Later that day a prolonged attack of pain developed, associated with sweating and nausea. This was followed by leucocytosis and slight increase of the sedimentation rate.

The first electrocardiogram (Fig. 7,*A*) was taken one day after the prolonged attack of pain. It shows right bundle branch block and features which indicate anterior infarction. A small Q wave is present in Lead I; Q waves of significant size are observed in Leads CR_3 and CR_4. Tracings *B* through *D*, which were taken in intervals of several days, show progressive changes. T_1 becomes flat and is later inverted, while the amplitude of T_3 increases. In the chest leads the T waves show progressive inversion. The amplitude of the inverted T waves in Leads CR_2 through CR_4 (in tracing *D*) is almost 15.0 millimeters. Tracings *E* and *F* show regressive changes. In tracing *F*, which was taken eighteen months after the attack, the Q waves have markedly decreased in size. However, the pattern T_1 lower than T_3 persists.

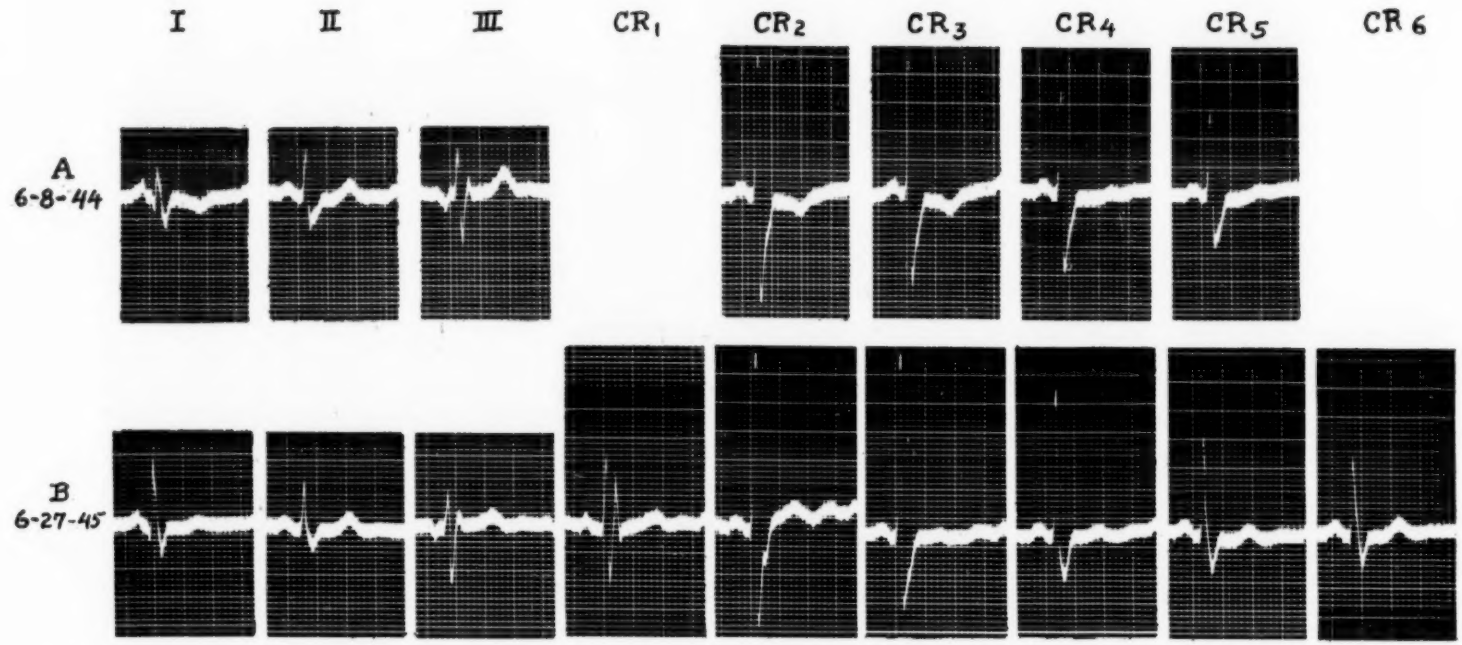

Fig. 6.—Case 5. *A*, electrocardiogram made after two attacks of mild anginal pain which occurred within twenty-four hours. The tracing shows right bundle branch block; in addition, there are changes which suggest anterior infarction. Q_1 is one-fourth the size of R_1. T_1 is inverted; T_3 is unusually high. In Leads CR_2 and CR_3, the T waves are inverted; in Leads CR_4 and CR_5, the T wave is diphasic and low. *B*, one year after *A*. The changes due to infarction are regressive. In Lead I, the amplitude of the R wave has increased. T_1 has become upright, but is lower than T_3. In the leads from the right side of the precordium, the T waves have become mainly upright. In leads from the left of the precordium, the amplitude of the T wave has increased.

Summary: Anterior infarction complicating right bundle branch block was indicated by significant Q waves which were followed by late R deflections, and by progressive inversion of T waves. The unusually high T waves in Lead III were diagnostically significant, as were inverted T waves of large amplitude in the chest leads. The pattern T_1 lower than T_3 persisted after the significant changes of the QRS complex had disappeared.

POSTERIOR INFARCTION WITH RIGHT BUNDLE BRANCH BLOCK

Our study includes fifteen patients with right bundle branch block for whom the diagnosis of posterior infarction was made. In two, the diagnosis was con-

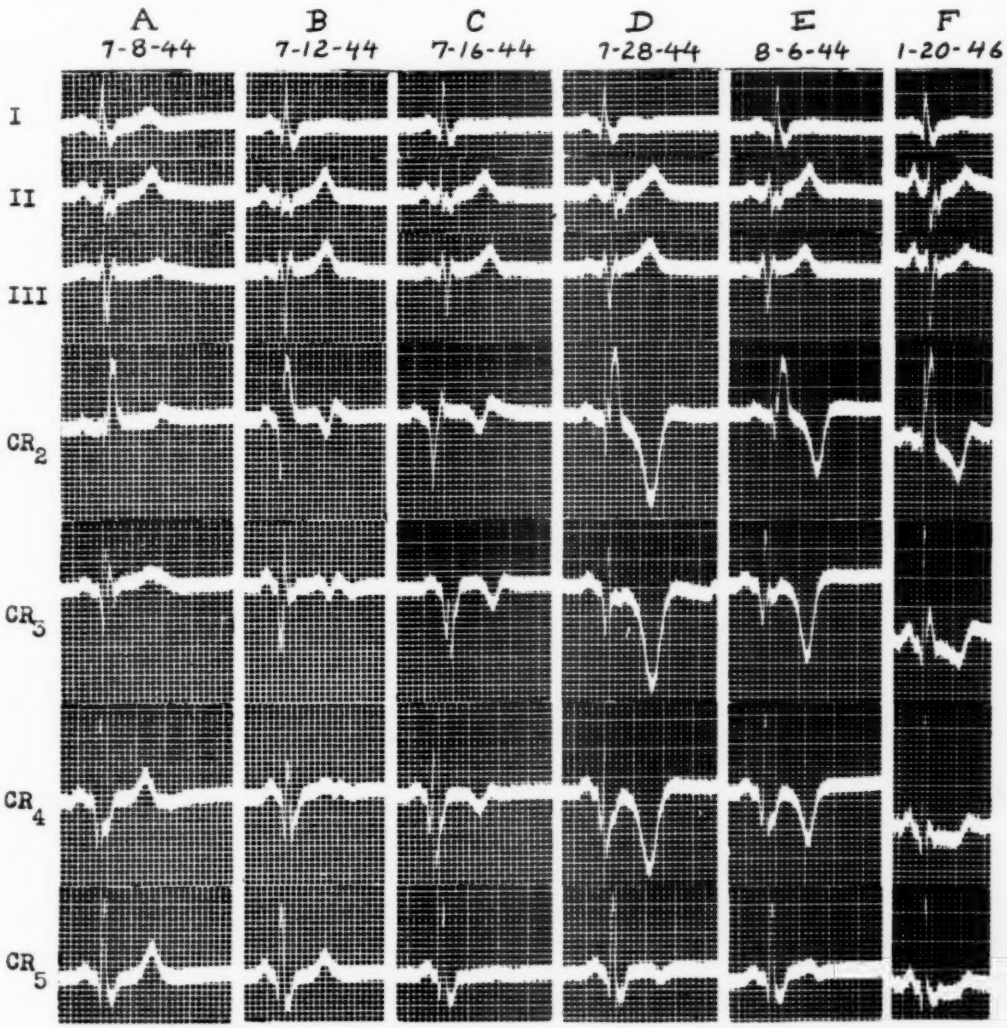

Fig. 7.—Case 6. *A*, electrocardiogram made one day after the coronary attack. The tracing shows right bundle branch block. Deep Q waves in Leads CR_3 and CR_4 suggest anterior-wall infarction. *B-D*, taken at intervals of several days. There is progressive inversion of the T wave in Lead I and in the chest leads; in Leads CR_2 through CR_4 the amplitude of the inverted T waves is almost 15 mm. (in tracing *D*). *E*, four weeks after the attack. The changes are regressive. *F*, eighteen months after the attack. The significant changes of the QRS complex have disappeared, but the pattern T_1 lower than T_3 persists.

firmed by post-mortem examination. In one, signs of posterior infarction were present prior to the development of right bundle branch block. In two, serial records showed progressive changes such as accompany recent posterior infarction. In the remaining ten patients the diagnosis of infarction was supported by clinical and laboratory findings.

CASE 7.—B. H., a 48-year-old man, had a history of high blood pressure of a few years' duration. In February, 1947, after a "cold," he complained of frequent, transient pains in the epigastric region and chest. An electrocardiogram (Fig. 8,*A*), taken on March 4, 1947, showed features of right bundle branch block. In spite of recurrent attacks of pain, the patient worked as usual. On March 12, 1947, he had an attack of unusually severe pain which lasted for several hours and required the administration of morphine.

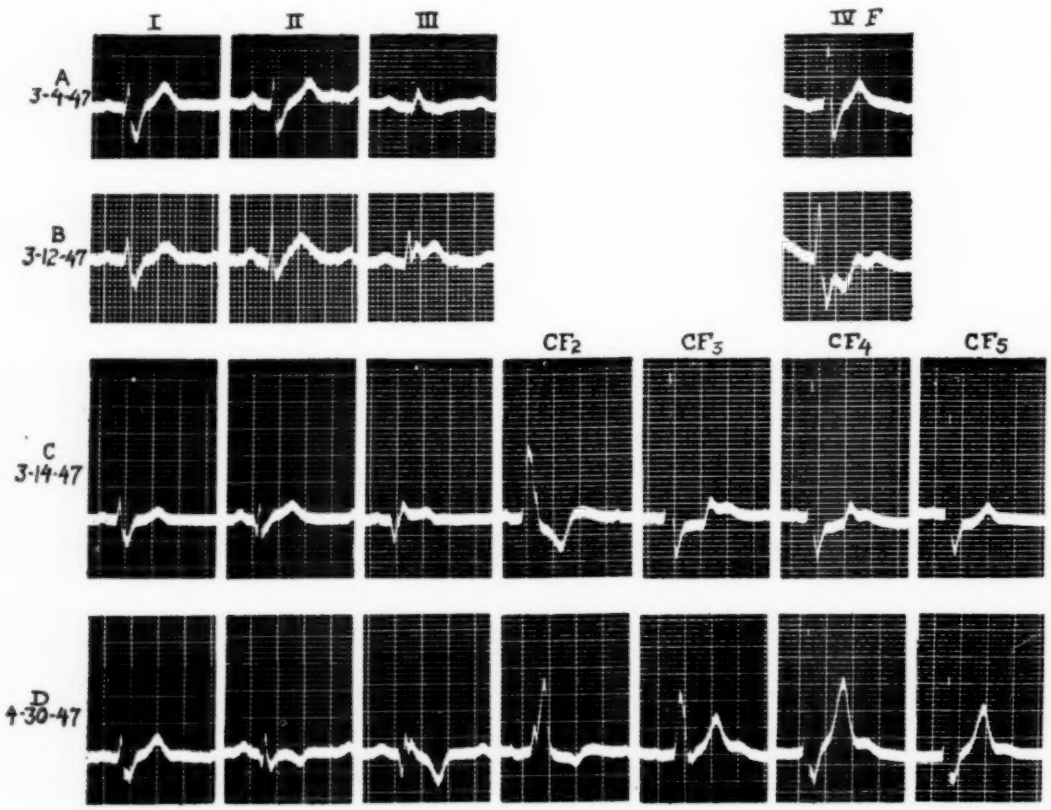

Fig. 8.—Case 7. *A*, electrocardiogram made one week before the cardiac infarction. Right bundle branch block is present. *B*, on the day of the coronary attack. In Lead III, marked elevation of the RS-T segment is associated with a high T wave. Lead IV_F shows a depressed RS-T segment and semi-inverted T wave. *C*, two days after the attack. Significant Q waves are present in Leads II and III. T_3 is semi-inverted. There is depression of the RS-T segment in the chest leads. *D*, seven weeks after the attack. T_2 and T_3 are inverted. The amplitude of T_3 is 5.0 millimeters. In the chest leads, depression of the RS-T segment has disappeared and the height of the upright T waves has markedly increased. The changes are diagnostic of recent posterior infarction.

Tracing *B* (Fig. 8) was taken several hours after the onset of the prolonged attack of pain. It shows, in addition to right bundle branch block, abnormal elevation of the RS-T junction associated with a high T wave in Lead III. In Lead IV_F, the RS-T junction is markedly de-

pressed, and the T wave is mainly inverted and followed by a conspicuous U wave. Tracing *C* was taken two days after the attack. Significant Q waves have appeared in Leads II and III. T_3 is lower and diphasic (±). The chest leads CF_3 through CF_5, which present the left-side pattern, show unusual depression of the RS-T segment. Tracing *D*, taken seven weeks after the attack, shows further changes. T_2 and T_3 have become inverted. The amplitude of T_3 is 5.0 millimeters. In the chest leads, depression of the RS-T segment has disappeared, and the amplitude of the upright T waves has markedly increased.*

Summary: Right bundle branch block was present prior to cardiac infarction. Following it, serial tracings showed the development of significant Q waves and progressive inversion of T waves in Leads II and III, characteristic of posterior infarction.

CASE 8.—J. S. was a 70-year-old man. He had a history of five years' duration of precordial pressure when he walked only one-half block. On April 10, 1945, while walking, he had unusually severe chest distress which persisted even when he rested. This attack was followed by rise in temperature and increase of the sedimentation rate.

The first electrocardiogram (Fig. 9,*A*) was taken on the day of the heart attack. It shows the pattern of right bundle branch block and features characteristic of posterior infarction. In Lead III, the RS-T junction is abnormally elevated and is followed by a plus-minus T. Reciprocal changes are seen in Lead I. Lead II shows a significant downward deflection of the QRS complex which is preceded by a tiny upstroke (Q-wave equivalent). In Leads CF_3 and CF_5, marked depression of the RS-T junction is associated with almost complete inversion of the T wave. Tracing *B* was taken nine days after the attack. In Lead II a significant Q wave is present; this indicates that the deep minus deflection of the QRS complex in Lead III, which is preceded by a slight upstroke, represents a Q-wave equivalent. T_2 and T_3 are inverted. In the chest leads, depression of the RS-T junction is diminished.

The patient was readmitted to the hospital on Jan. 3, 1947, after he had another prolonged attack of precordial pain. The electrocardiogram (Fig. 9, *C*) shows the unequivocal features of posterior infarction superimposed on right bundle branch block. Significant Q waves and inverted T waves are present in Leads II and III. The amplitude of the inverted T_3 is 5.0 millimeters. The chest leads (except CF_1) show fairly high T waves with depressed RS-T segments.

Summary: There were two attacks of cardiac infarction, one in 1945 and one in 1947. Each time the electrocardiogram showed, in addition to right bundle branch block, the signs of posterior infarction. At times, Q-wave equivalents were present in Leads II and III.

COMBINED ANTERIOR (LATERAL) AND POSTERIOR INFARCTIONS WITH RIGHT BUNDLE BRANCH BLOCK

The group of combined anterior (lateral) and posterior infarctions includes twenty patients; there are three instances of posterolateral infarction and seventeen of infarctions of both anterior and posterior site. The latter series includes four patients in whom post-mortem examination revealed infarction of the interventricular septum which extended from the anterior to the posterior aspect of the heart and involved varying portions of the anterior and posterior walls of the left ventricle. The diagnosis of myocardial infarction was confirmed by post-mortem examination of six patients. In two instances, myocardial infarction was indicated by changes in tracings which were obtained prior to the development of bundle branch block, or after its disappearance. In five, serial records showed progressive changes which corroborated the diagnosis of myocardial infarction. In the remaining seven the diagnosis of infarction was supported by clinical and laboratory findings.

*We are indebted to Dr. Hans Gottlieb, Brooklyn, for the permission to use these tracings.

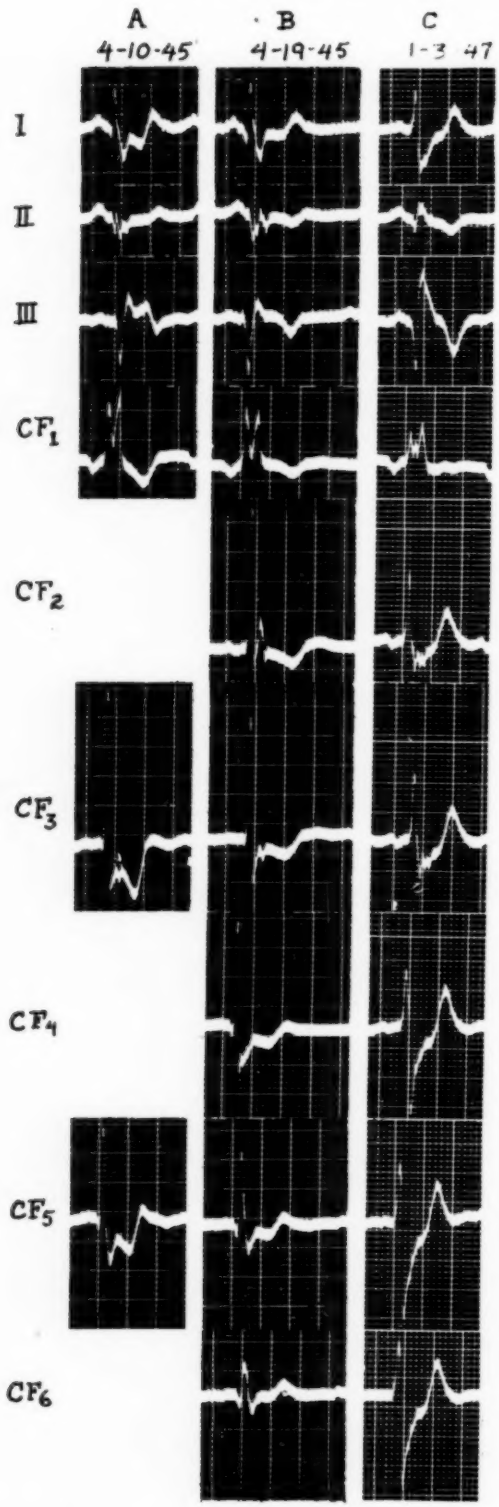

Fig. 9.—(For legend, see opposite page.)

CASE 9.—A. C., a 46-year-old man, was first examined on Oct. 21, 1940, when he complained of abdominal discomfort. Roentgenologic examination suggested duodenal ulcer. At that time there was slight dyspnea but no angina pectoris. The blood pressure was 145/100. The left ventricle was slightly enlarged. The electrocardiogram (Fig. 10,*A*) shows a low R_1 and prominent S waves in Leads II and III. The duration of the QRS complex is normal. The finding of a Q wave in Lead CF_2 is unusual.

The second electrocardiogram (Fig. 10,*B*) was taken two years later, after the patient had three attacks of squeezing precordial pain within five days, each attack lasting for several hours; the attacks were followed by rise in temperature, leucocytosis, and increase of the sedimentation rate. The tracing shows changes diagnostic of anterior infarction. The changes are further advanced in tracing *C*, which was taken eleven days after *B*.

On May 10, 1946, the patient was readmitted to the hospital because of severe, prolonged attacks of anginal pain which had occurred two days previously. They were followed by low-grade fever, increase of the sedimentation rate, and fall of the blood pressure. An electrocardiogram taken on May 11, 1946, (Fig. 10,*D*) shows the features of right bundle branch block and, as previously, the pattern r_1 S_2 S_3. S_2 measures ten times the amplitude of R_2. The RS-T junction is slightly depressed in Lead I, and elevated in Lead III. T_1 is upright, T_2 is diphasic, and T_3 is inverted. The chest leads show wide, slurred Q waves which are of significant size in Leads CF_2 through CF_6; in the leads from the right side of the precordium the Q waves are followed by late R deflections. In all precordial leads, the RS-T junctions are slightly depressed and followed by upright T waves. The changes of the QRS complex in the chest leads are suggestive of anterior infarction. The reciprocal changes of the RS-T segments and T waves in the limb leads may arouse suspicion of posterior-wall involvement. Tracing *E*, which was taken on May 15, 1946, shows slight changes. T_2 and T_3 are mainly upright. In Leads CF_1 through CF_3, wide and slurred Q waves are noted. The T waves are inverted in leads from the right side of the precordium.

The patient died on July 23, 1946. Post-mortem examination revealed an enlarged heart that weighed 650 grams. The left ventricle showed three areas of infarction. One area, 3 cm. in diameter, was in the basal region of the posterior wall encroaching upon the septum; it showed recent subendocardial necrosis. Another infarction, somewhat older, occupied the apical portions of both the anterior and posterior walls. It measured about 2 cm. in diameter. Signs of advanced organization suggested that this infarction could have occurred about two months prior to death, that is, in May, 1946. An old infarction, which consisted entirely of fibrous tissue, occupied the midportion of the anterior wall.

Summary: Signs of anterior infarction were present prior to the development of right bundle branch block (tracings *B* and *C*). They were probably due to an infarction of the midportion of the anterior wall, which was found at post-mortem examination four years later. Another infarction developed four years after the first; at that time the electrocardiogram (tracings *D* and *E*) showed right bundle branch block and some features which suggested involvement of the posterior wall in addition to the old signs of anterior infarction. The second attack was probably caused by a small infarction, found at post-mortem examination, which involved the anterior and posterior walls of the left ventricle in the apical region. A third area of subendocardial necrosis in the basal portion of the posterior wall was of recent origin and may have occurred after the last electrocardiogram (*E*) was taken.

Fig. 9.—Case 8. *A*, electrocardiogram made on the day of the first coronary attack. Signs of recent posterior infarction are superimposed on right bundle branch block. In Lead III the RS-T junction is significantly elevated, and the T wave is diphasic (±). Lead I shows reciprocal changes. In Lead II a deep minus deflection of the QRS wave is preceded by a tiny upstroke (Q-wave equivalent). Similar features of the QRS complex are noted in Lead III. In Leads CF_3 and CF_5, marked depression of the RS-T junction is associated with almost complete inversion of the T wave. *B*, nine days after the attack. Lead II shows a deep Q wave; this suggests that the deep downward deflection of the QRS complex in Lead III is a Q-wave equivalent. T_2 and T_3 are inverted. There is less depression of the RS-T segment in the chest leads. *C*, two years later, after a new coronary attack. The signs of posterior infarction are even more pronounced than previously. Significant Q waves and inverted T waves are present in Leads II and III. The amplitude of the inverted T_3 is 5.0 millimeters. In the chest leads, depression of the RS-T segments is associated with fairly high T waves.

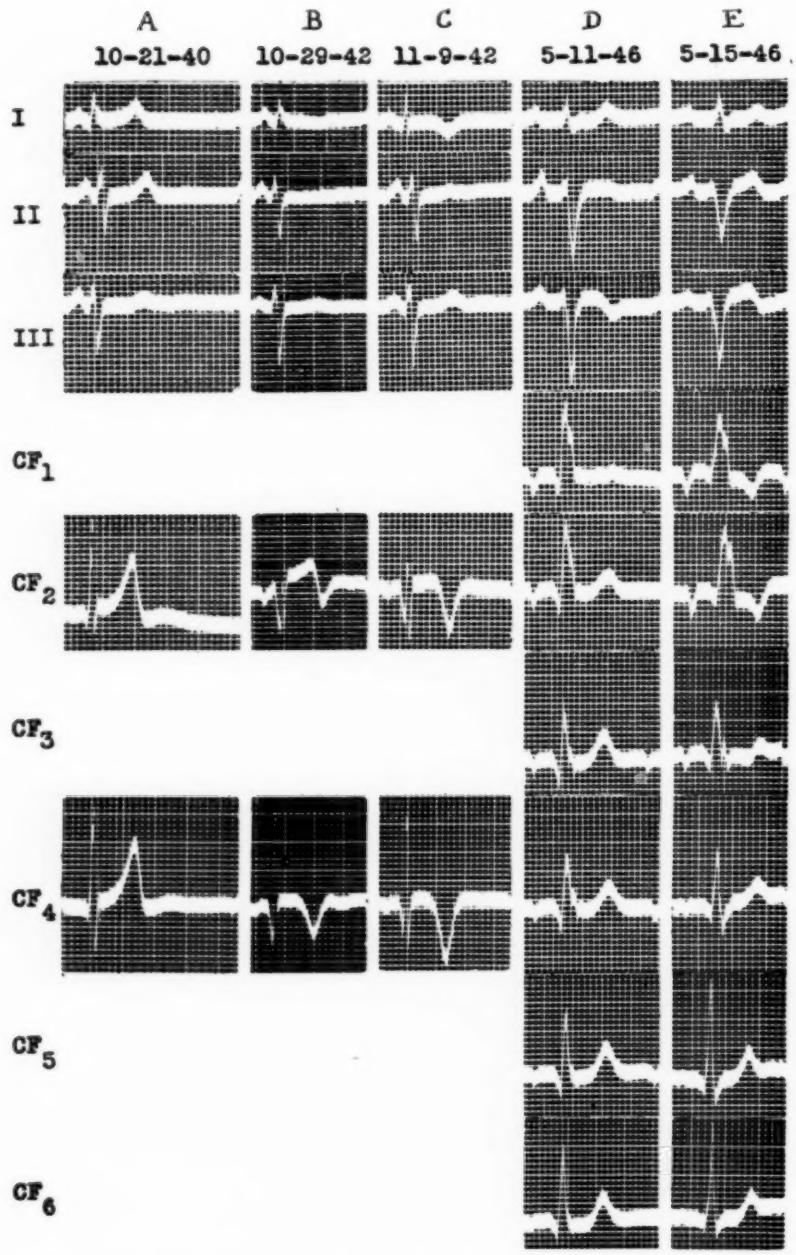

Fig. 10.—Case 9. *A*, electrocardiogram made before the coronary attack. The QRS complex is of normal duration and shows the pattern r_1 S_2 S_3. A Q wave in Lead CF_2 is unusual. *B*, two years later. Repeated attacks of precordial pain have occurred. Inversion of T_1 and, in the chest leads, significant Q waves and inversion of the T waves indicate anterior infarction. *C*, eleven days after *B*. Inversion of the T waves in Lead I and in the chest leads is more marked. *D*, four years later; attacks of severe anginal pain occurred on May 8, 1946. There is now right bundle branch block. The pattern r_1 S_2 S_3 is even more pronounced. In Lead III the RS-T junction is slightly elevated and the T wave is inverted. Reciprocal changes are present in Lead I. T_2 is diphasic (±). These changes may be due to posterior wall involvement. Wide and slurred Q waves in the chest leads suggest anterior infarction. *E*, four days after *D*. T_2 and T_3 are mainly upright; in the precordial leads from the right side the T waves are inverted.

CASE 10.—J. S., a 64-year-old man, had a history of effort angina of one year's duration. On Nov. 15, 1947, he had a severe attack of precordial pain, and cold sweat, followed by fever, marked leucocytosis, and drop in blood pressure. Six days after the first attack substernal pain recurred, accompanied by weakness and profuse perspiration. The patient died on Nov. 25, 1947.

The first electrocardiogram (Fig. 11,*A*) was taken four hours after the onset of chest pain. It shows the pattern of right bundle branch block with deep S waves in Leads II and III. Small Q waves are present in Leads CR_1 through CR_4, but none in CR_5 and CR_6. This is a reversal of the usual conditions. The RS-T junction is elevated in Leads CR_1 and CR_2, and unusually depressed in the leads from the left side of the precordium and in Leads II and III. The first limb of the T wave is upward convex and there is notching of the T wave in Leads CR_1 and CR_2. The reciprocal deviations of the RS-T segment in leads from the right and left sides of the precordium are suggestive of an early stage of anteroseptal infarction.[4]

Tracing *B* was taken twenty-two hours after the attack. The voltage of R_1 has decreased and the pattern $S_1\ S_2\ S_3$ is present. In Lead I the RS-T junction is abnormally elevated and the T wave is inverted. T_3 is unusually high. In Leads CR_1 through CR_3 the amplitude and width of the Q waves have increased; simultaneously, the size of the R wave has decreased in all chest leads but CR_1. The RS-T junction is elevated in all precordial leads. The T wave is inverted in Leads CR_1 through CR_4, and diphasic (±) in Leads CR_5 and CR_6.

Tracing *C* was taken two days after the onset of chest pain. It shows more marked inversion of the T wave in leads from the right side of the precordium; in leads from the left side the T waves are entirely upright and of increased amplitude.

Tracing *D* was taken six days after the onset of the first attack, when anginal pain recurred. New myocardial ischemia is indicated in the electrocardiogram by increased elevation of the RS-T junction in leads from the right side of the precordium and in Lead I. The augmented unipolar limb leads show the factors which contribute to the development of the pattern $S_1\ S_2\ S_3$. The R wave is unusually high in Lead aV_R, and low in aV_L. Lead aV_L resembles the leads from the right side of the precordium; Lead aV_F equals Lead CR_6. Hence, the heart is in semivertical position. The deep S wave in the left leg lead and the high R deflection in the right arm lead, in conjunction with a low R wave in Lead aV_L, cause the major deflection to be directed downward in all limb leads.

Post-mortem examination revealed left ventricular hypertrophy; the heart weighed 450 grams. A recent extensive infarction occupied the whole anterior wall of the left ventricle from apex to base; it extended to the lateral wall, and involved the lower third of the interventricular septum and the apical region of the posterior wall. Rupture of an area of necrotic myocardium in the anterolateral region had caused cardiac tamponade.

Summary: Following the first attack of chest pain, the electrocardiogram showed right bundle branch block and signs of anteroseptal infarction. Simultaneously the pattern $S_1\ S_2\ S_3$ developed. Another attack of chest pain occurred four days before death. Post-mortem examination revealed a vastly more extensive infarction than was expected on the basis of the electrocardiographic changes. It is reasonable to assume that further extension of the infarction occurred after the last electrocardiogram was taken (four days before death), which showed new signs of an acute ischemic process.

CASE 11.—W. S., a 71-year-old man, was admitted to the hospital because of urinary obstruction on Dec. 7, 1946. A "heart attack" had occurred two years previously. During the few weeks prior to hospitalization the patient had repeated attacks of dyspnea during the day and night. On admission he was stuporous and in a preuremic condition. The blood urea nitrogen was 48 mg. per 100 cubic centimeters. The blood pressure was 170/90. Cystotomy was performed on Dec. 9, 1946. The patient became restless and irrational. He died on Dec. 19, 1946.

The first electrocardiogram (Fig. 12,*A*) was taken on Dec. 8, 1946. It shows right bundle branch block. In Lead I, a significant Q-wave equivalent is present and the T wave is inverted. Leads II and III show prominent S deflections. In Lead II, a tiny upstroke precedes the deep negative deflection. This suggests that the negative QRS deflections in Lead II and in Lead III may represent Q-wave equivalents. Small Q waves are present in all chest leads except CF_1.

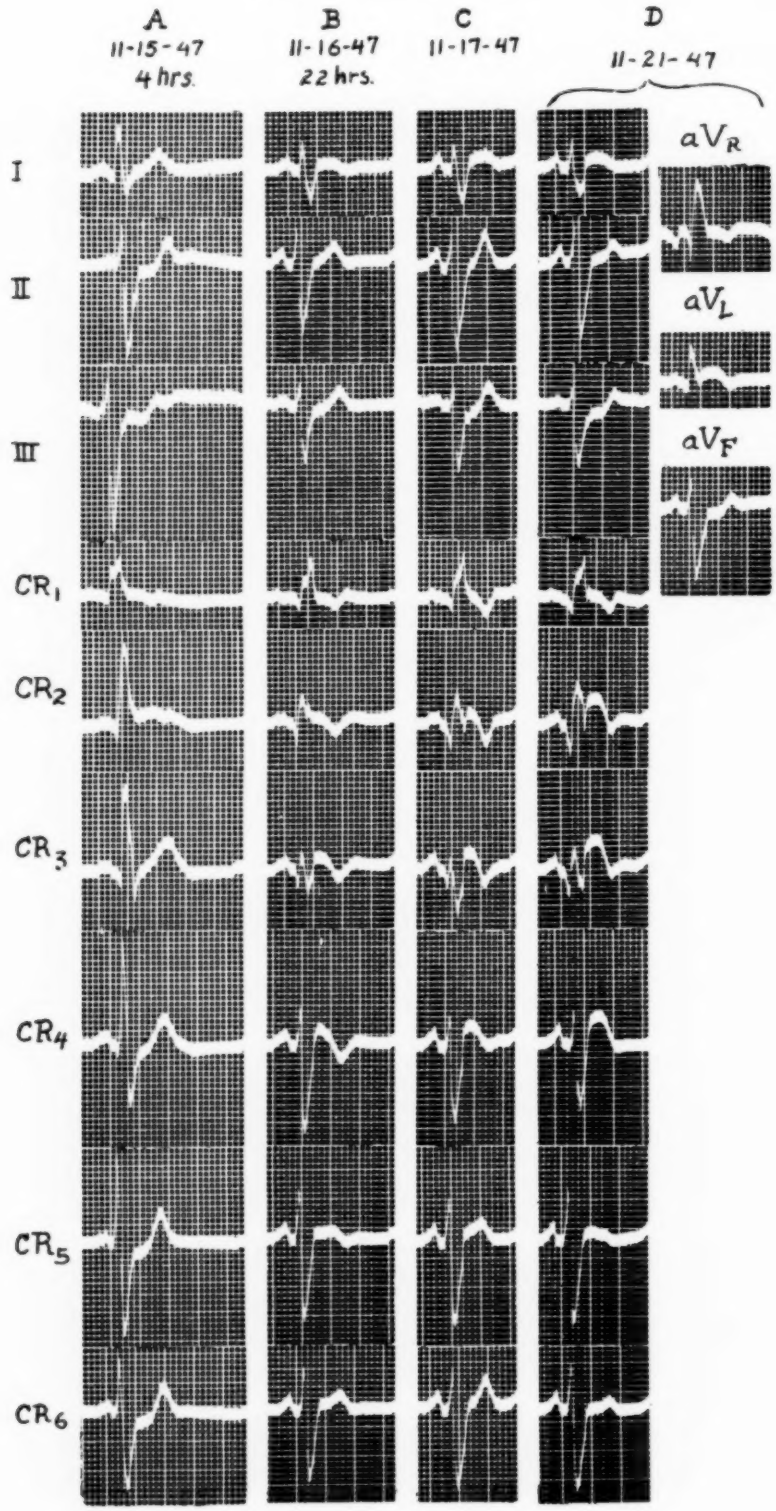

Fig. 11.—(For legend, see opposite page.)

The T waves are upright in the precordial leads from the right side, and inverted in the leads from left-side positions. The changes in the limb and chest leads suggest infarction of posterior and anterolateral location. Tracing *B* was taken on Dec. 11, 1946, two days after the operation. The limb leads show the pattern $S_1 S_2 S_3$ associated with low voltage of QRS. A significant Q wave is present in Lead I. T_1 has turned upright. In Leads II and III a very small upstroke precedes the downward deflection of the QRS complex. The chest leads show changes indicative of recent anterior infarction. In Leads CF_2 through CF_6 the Q waves, which were previously present, have become deeper, wider, and slurred; the amplitude of the R waves has decreased; there is significant elevation of the RS-T segment with a terminal inversion of the T wave. In tracing *C*, taken on Dec. 13, 1946, the amplitude of the Q deflections and inverted T waves in the chest leads has increased.

Post-mortem examination revealed a recent infarction that involved the lower half of the interventricular septum, an adjacent portion of the anterior wall, and the lower third of the posterior wall of the left ventricle. Extensive scarring was present in the upper two-thirds of the posterior and lateral walls of the left ventricle.

Summary: An old posterolateral infarction (proved by post-mortem examination) was indicated in the first electrocardiogram (Fig. 12,*A*) by Q-wave equivalents in all limb leads and by inversion of the T waves in Lead I and in the leads from the left side of the precordium. A recent anteroseptal infarction was indicated in tracings *B* and *C* (Fig. 12) by progressive changes of the QRS complexes and T waves in the chest leads. Recent involvement of the posterior wall did not significantly alter the electrocardiographic picture.

CASE 12.—W. G., a 56-year-old man, had a history of burning pain in the precordium in conjunction with effort or excitement of a few years' duration. On Nov. 21, 1946, while walking in the morning, he developed unusually severe pain across the chest; this was not, as usual, relieved by nitroglycerin. The pain recurred repeatedly until morphine was administered. After the attack, increase of the sedimentation rate was observed.

The first electrocardiogram (Fig. 13,*A*) was obtained one week after the attack. It shows the pattern of right bundle branch block and signs suggestive of posterolateral infarction. Lead I presents a rather broad Q wave. In Lead II, a large negative deflection of the QRS complex is preceded by a tiny upstroke. This is apparently a Q-wave equivalent and suggests that the deep downward deflection in Lead III has similar significance. The T wave is notched in Lead II, and inverted in Lead III. Leads CR_6 and CR_7 show significant, deep Q waves and elevation of the RS-T junction; reciprocal depression of the RS-T segment is present in Leads CR_1 through CR_4. Tracings *B*, *C*, and *D* were taken at intervals of several days. They demonstrate progressive inversion of T waves in Leads II and III, and in CR_5 through CR_7; simultaneously, the amplitude of the T wave has increased in the leads from the right side of the precordium.

Summary: Following an attack of chest pain the electrocardiogram showed, superimposed on the pattern of right bundle branch block, changes of the QRS and T waves, diagnostic of posterolateral infarction.

Fig. 11.—Case 10. *A*, electrocardiogram made four hours after the coronary attack. The pattern of right bundle branch block is present. Leads II and III show deep S waves and marked depression of the RS-T segments. In Leads CR_1 through CR_4, small Q waves are present. There is elevation of the RS-T segment in the leads from the right side of the precordium, and unusual depression of the RS-T segment in the leads from the left side. Such reciprocal deviations of RS-T are observed in the acute stage of anteroseptal infarction. *B*, twenty-two hours after the onset of the attack. In Lead I, the RS-T segment is elevated and upward convex, and the T wave is inverted. T_3 is unusually high. In Leads CR_1 through CR_3, the Q waves have become wider and deeper. The amplitude of the R wave has decreased in all chest leads but CR_1. The RS-T junctions are now elevated in the precordial Leads CR_2 through CR_6. The T wave is inverted in Leads CR_1 through CR_4, and diphasic in CR_5 and CR_6. *C*, two days after the attack. Inversion of the T wave is more marked in Leads CR_1 through CR_3; T is upright in CR_5 and CR_6. *D*, six days after the attack; anginal pain recurred. There is more marked elevation of the RS-T segment in Leads CR_1 through CR_4, suggesting a new acute ischemic process. The unipolar limb leads show an unusually high R wave in Lead aV_R, and a low R deflection in Lead aV_L. Lead aV_F presents a deep S wave and resembles Leads CR_5 and CR_6.

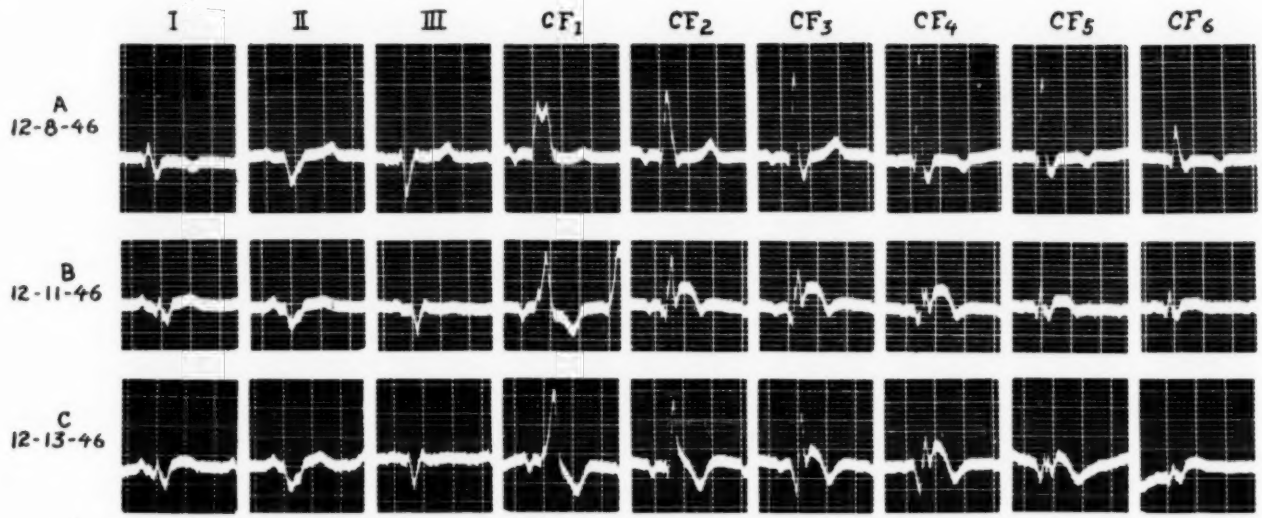

Fig. 12.—Case 11. *A*, the tracing shows the pattern of right bundle branch block and signs suggestive of posterolateral infarction. Q-wave equivalents are present in Leads I and II. The finding of a Q-wave equivalent in Lead II suggests that the downward QRS deflection in Lead III may be also a Q-wave equivalent. The T waves are inverted in Lead I and in Leads CF_4 through CF_6. *B*, three days after *A* (two days after an operation). Lead I shows a significant Q wave. In Leads II and III, only a tiny upstroke precedes the negative deflection of QRS. In all limb leads the major QRS deflection is directed downward (pattern S_1 S_2 S_3) and is of low voltage. Leads CF_2 through CF_6 show signs of recent anterior infarction: significant, wide and slurred Q waves, decreased amplitude of R waves, and abnormal elevation of the RS-T segment with partial inversion of the T wave. In Leads CF_2 through CF_4 the Q waves are followed by late R deflections. *C*, two days after *B*. In the chest leads the Q waves are deeper, and inversion of the T waves is more marked.

DISCUSSION

In the presence of right bundle branch block conditions are more favorable for the diagnosis of myocardial infarction than when the obstructive lesion is in the left division of the bundle. Right bundle branch block does not change the spread of the excitation in the left ventricle. The potential of the cavity of the left ventricle is negative throughout the time of activation, and is transmitted to the exploring electrode overlying those parts of the ventricular wall which have become incapable of responding to the excitatory process because of extensive necrosis. Thus, deep Q waves or QS deflections may be recorded when myocardial infarction is present.

Anterior Wall Infarction.—

Changes of QRS: Rosenbaum and associates[1] studied, in dogs, the changes of the QRS complex caused by anterior infarction in the presence of right bundle branch block. In precordial leads taken from the infarcted area either deep Q waves or QS deflections were observed. In leads from the right side of the precordium, deep Q waves preceded late R waves. The Q waves were due to potential variations transmitted from the infarcted area, while the late R waves were caused by the delayed activity of the intact wall of the right ventricle. Similar observations can be made in man.

When right bundle branch block is uncomplicated, Q waves are often present in the limb leads and in those precordial leads presenting the left-side pattern. As may be expected, Q waves are usually absent in leads from the right side of the precordium because the excitation spreads from the left to the right ventricle through the interventricular septum. Therefore, electrodes placed over the intact wall of the right ventricle are facing the head of the excitation wave at the beginning of systole. Occasionally, however, in the canine electrocardiogram and exceptionally in man, Q waves are inscribed in leads from the right side of the precordium in the presence of right bundle branch block.[1] Their origin is obscure. They may be due to a congenital variation in the distribution of the intraventricular conduction fibers or to block in ramifications of the left bundle branch, which causes some parts of the left ventricle other than the interventricular septum to be activated first; therefore, an electrode placed over the uninjured wall of the right ventricle may face, at the beginning of systole, the tail instead of the head of the excitation wave. In our series of thirty-two patients with uncomplicated right bundle branch block, Q waves were observed in Leads C_1 and C_2 in one instance. They showed features similar to the Q waves occurring in the other chest leads and in Lead I, in the absence of myocardial infarction. Their amplitude was less than one quarter of that of the succeeding R wave; their duration was less than 0.04 second, and they did not show conspicuous slurring or notching.

When right bundle branch block is complicated by anterior infarction, significant Q waves in Lead I and in the chest leads may show the following features: (1) their amplitude is one-fourth or more of the amplitude of the R wave in the same lead; (2) their duration is 0.04 second or longer; (3) they may show conspicuous slurring or notching; (4) the very presence of Q waves in leads from the right side of the precordium should arouse suspicion of anteroseptal infarction (Fig. 10, *D* and *E*; Fig. 11).

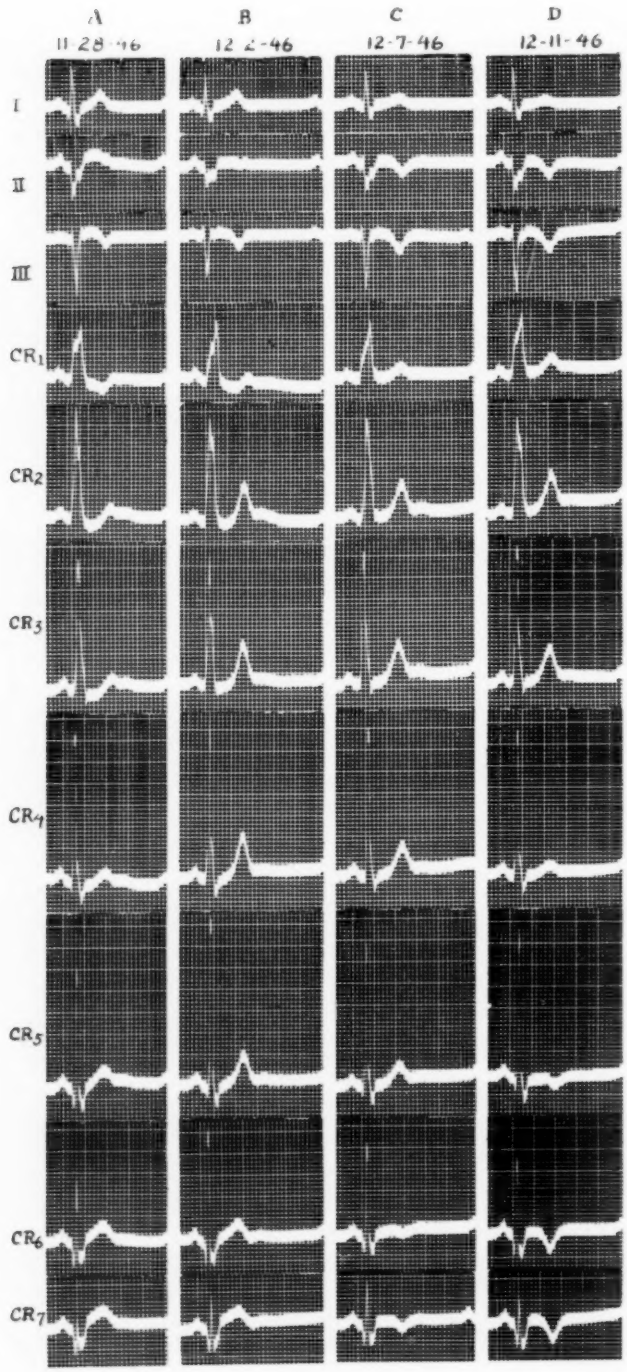

Fig. 13.—(For legend, see opposite page.)

In some cases of myocardial infarction, significant negative deflections of the QRS complex are preceded by small positive deflections.[5] When right bundle branch block is present, it may be difficult to distinguish such Q-wave equivalents from deep S deflections which, in leads from the right side of the precordium, separate a small initial upstroke from late R′ deflections in the absence of infarction. In our group of thirty-two patients with uncomplicated right bundle branch block, a low R deflection, measuring 2 mm. or less, was observed in Lead C_1 in eleven patients, in Lead C_2 in three, and once in Lead C_3. The smallest amplitude of the R wave in these leads was 0.6 mm.; the average ratio of the amplitude S/R was five, and the maximum ratio was eleven (observed in one tracing in Lead C_2). A Q-wave equivalent in Leads C_1, C_2, and C_3 may be suspected to be present when the R deflection measures 0.5 mm. or less and the ratio of amplitude S/R is ten or more. The lower the R deflection and the deeper the S wave, the greater is the likelihood that a Q-wave equivalent is present. In leads from the left side of the precordium, Q-wave equivalents can be readily distinguished from ordinary RS complexes, because when right bundle branch block is uncomplicated, the minimum amplitude of the R waves in these leads is well above the size of the initial upstroke which is part of a Q-wave equivalent. In the group with uncomplicated right bundle branch block, the lowest R wave in leads from positions C_4, C_5, and C_6 measured 4.0 millimeters. The average amplitude of the R wave was far above this value; in Leads C_4 and C_5, it measured 14 mm., in Lead C_6, 10 millimeters. Thus, in leads from the left side of the precordium, an R deflection may be considered significantly low when its amplitude is 3.0 mm. or less. Q-wave equivalents can be seen in Fig. 4, *C* and *D*.

A QRS pattern consisting of a low R deflection in Lead I and prominent S waves in Leads II and III (r_1, S_2 S_3) has been described as a feature of anterior infarction.[6,7] This pattern is often accompanied by a conduction disorder in the right bundle branch and it usually indicates extensive infarction.[8] In thirty-two patients with uncomplicated right bundle branch block, the pattern r_1 S_2 S_3, with an R_1 deflection measuring less than 5.0 mm., was never observed. On the other hand, in forty-five patients with right bundle branch block complicated by either anterior (lateral) or by anterior and posterior infarctions, the pattern r_1 S_2 S_3 was encountered in nine patients (20 per cent), three of whom died shortly after the cardiac infarction (Fig. 10). Post-mortem examination revealed massive infarction involving the anteroseptal wall in one instance, and the anterior and posterior walls in two. The high percentage (33 per cent) of early death in patients with infarction who showed the pattern r_1 S_2 S_3 is in accord with figures reported by others.[8]

Fig. 13.—Case 12. Electrocardiogram made one week after the coronary attack. Superimposed on the pattern of right bundle branch block, there are signs of posterolateral infarction. In Leads II and III, the chief QRS deflection is directed downward. It is preceded, in Lead II, by a tiny upstroke. This suggests that the negative deflection in Lead II is a Q-wave equivalent, and that S_2 may have similar significance. T_2 is notched; T_3 is inverted. Leads CR_6 and CR_7 show significant Q waves and elevation of the RS-T junction; a reciprocal depression and a downward bow of the RS-T segment are observed in the leads from the right side of the precordium. Tracings *B-D* were taken at intervals of several days. They show progressive inversion of T waves in Leads II and III, and in CR_5 through CR_7. Reciprocal increase in the height of the T wave is shown in the leads from the right side of the precordium.

The pattern r_1 S_2 S_3 resembles another QRS pattern (in fact, one pattern may change to the other) which may also be associated with myocardial infarction and right bundle branch block. This is characterized by prominent downward deflections in all limb leads (S_1 S_2 S_3). This pattern was observed in one of thirty-two patients (3 per cent) with uncomplicated right bundle branch block, and in seven of forty-five patients (16 per cent) with right bundle branch block complicated by either anterior infarction or by infarctions of anterior and posterior location (Figs. 11, *B-D*, and 12). The incidence of this pattern in patients with infarction (16 per cent) is slightly less than the frequency of the pattern r_1 S_2 S_3 (20 per cent). Early death occurred in four of the seven patients with infarction who presented prominent negative deflections in all limb leads. This pattern is of particular significance when it is associated with low voltage of the QRS complex in the limb leads. In fact, it was described as almost pathognomonic of anterior infarction.[7] This feature was not observed in our patients with uncomplicated right bundle branch block. Low voltage of QRS was present in three of the seven patients with infarction who showed prominent negative deflections of the QRS complex in all limb leads (see Figs. 3 and 12). The mortality in these three patients was 100 per cent. In two of them, post-mortem examination was performed and revealed massive infarction, which in one instance (Case 2) involved the anteroseptal wall and resulted in a huge aneurysm; and in the other, (Case 11) occupied the posterolateral and anteroseptal walls of the left ventricle.

Changes of the RS-T Segment (First Limb of T): In the group with uncomplicated right bundle branch block, upright T waves, as a rule, showed a slight downward bow of the RS-T segment (first limb of the T wave). This was invariably so in Leads I and C_6. In leads from the transitional zone (C_3, C_4, and C_5), a straight RS-T segment was occasionally observed with upright T waves in the absence of infarction. A straight course of the RS-T segment (first limb of the T wave) in association with an upright T wave is suggestive of anterior (lateral) infarction, when it occurs in Lead I or in leads from the extreme left side of the precordium. The evidence is even more convincing when the first limb of the T wave shows an upward bow or when the T wave is dome-shaped.

Elevation of the RS-T junction in Lead I is suggestive of anterior infarction when it measures more than 1.0 millimeter. Elevation of the RS-T junction in Lead I and in the chest leads, measuring 1.0 mm. or more, is significant when it is associated with inverted or flat T waves, or when it is coupled with an upright T wave whose summit rises less above the level of the RS-T junction than the latter is elevated above the level of reference.

Depression of the RS-T junction in Lead III is significant when it measures more than 1.0 mm.; it may accompany anterior infarction as a reciprocal change.

Changes of the T Wave: Various significant changes of the T wave are observed in association with anterior infarction: (1) upright, low T waves in Lead I or in precordial leads from the left side, their amplitude measuring less than 1.0 mm.; (2) diphasic T waves of the plus-minus variety, or "coronary T waves" in Lead I or in the precordial leads; (3) inverted T waves, especially those of the

V type, occurring in Lead I or in the precordial leads from the left side. In leads from the right side of the precordium, which often show inversion of T waves in uncomplicated right bundle branch block, inverted T waves may be considered significant when their amplitude is 10.0 mm. or more (Fig. 7) or when they are associated with elevation of the RS-T junction measuring more than 1.0 millimeter.

When right bundle branch block is uncomplicated, upright T waves are infrequently present in Lead III. They were observed in less than one-fifth of our series of uncomplicated cases; their amplitude ranged from 0.5 to 1.8 millimeters. An upright T_3, which is higher than 2.0 mm., is likely to represent a reciprocal change due to anterior infarction.

Rosenbaum and associates[1] expressed the opinion that "block in the right side usually prevents the occurrence of characteristic signs of anterior infarction in the standard limb leads, but not in the precordial leads." Using the signs described above as suggestive of anterior infarction, we observed the following incidence of significant changes in twenty-five patients, for whom the diagnosis of anterior infarction was made (in four patients confirmed by necropsy): In the chest leads, significant changes of the QRS complex were present in twenty-two patients, and of ST-T in twenty-three patients. In Lead I significant changes of QRS and ST-T were observed in six; of QRS alone, in two; and of ST-T only, in thirteen patients. Significant changes were altogether absent in Lead I in four patients for whom anterior infarction had been diagnosed.

Posterior Infarction.—

Our experience with patients having posterior infarction is in accord with the view expressed by Rosenbaum and associates,[1] that block of the right bundle branch "does not seriously obscure the diagnostic signs of posterior infarction, which ordinarily appear in Leads II and III." Such diagnostic difficulties as may be encountered stem from two sources. First, deep Q waves and inverted T waves in Lead III are frequently a feature of uncomplicated right bundle branch block. Second, there is often the problem of differentiating Q-wave equivalents from the RS complexes which are occasionally observed in Leads II and III in the absence of posterior infarction.

Changes of the QRS Complex: A deep Q_3 was observed in about one-fifth of the patients with uncomplicated right bundle branch block, its amplitude measuring from one-third to double the size of R_3; occasionally Q_3 was also slurred and of increased duration (0.04 second or more). In uncomplicated right bundle branch block, a QS deflection was never observed in Lead III. The predominant configuration of QRS_3 was the M-shape. A W-shaped QRS complex was only exceptionally observed in Lead III; in that case, the amplitude of the R wave was a multiple of the size of the Q deflection.

A Q wave in Lead III is helpful in the diagnosis of posterior infarction when its duration is 0.04 second or more and when it shows marked slurring or notching; or when Q_3 is part of a QS deflection. A W-shaped QRS_3 is suggestive of posterior infarction when the R deflection does not exceed the amplitude of the Q wave.

A deep Q_3 alone has only limited diagnostic value, that is, chiefly by association with changes in other leads suggestive of posterior infarction. It is difficult to distinguish a Q-wave equivalent from a deep S_3 which may be found in uncomplicated right bundle branch block. The presence of a Q_3 equivalent is suggested, when a low R deflection and a deep S wave in Lead III are accompanied by a significant Q wave (or Q-wave equivalent) in Lead II.

A Q_2 was observed in about one-half of the patients with uncomplicated right bundle branch block. Its amplitude was less than one-fourth of the size of R_2, except in one tracing, where it equalled one-third of the amplitude of the succeeding R wave. A Q wave in Lead II is suggestive of posterior infarction when it is associated with a significant Q wave or Q-wave equivalent in Lead III, when its amplitude is at least one-fourth the size of R_2, when its duration is 0.04 second or more, and when it shows marked slurring or notching. The more of the above features are simultaneously present and, especially, the larger the ratio of amplitude Q_2/R_2 the greater is the diagnostic significance of a Q wave in Lead II.

In three patients with uncomplicated right bundle branch block, a deep S_2 was observed following a low R_2 deflection, the latter measuring from 0.9 to 1.9 mm.; the maximal ratio of amplitude S_2/R_2 was nine. Thus it may be quite difficult to distinguish RS complexes, which occur in Lead II in the absence of myocardial infarction, from significant Q-wave equivalents. The latter may be suspected to be present when the amplitude of R_2 is 0.5 mm. or less, and when the ratio of amplitude S/R is ten or more (Fig. 12). The lower the R deflection and the larger the ratio S/R, the more diagnostic significance may be attached to an RS complex in Lead II.

Changes of the RS-T Segment (First Limb of T): When the T waves are upright in Leads II and III, an upward directed bow of the first limb of the T wave is suggestive of posterior infarction.

Elevation of the RS-T junction in Lead III (and II) is significant when it measures 1.0 mm. or more. Its diagnostic significance is enhanced when it is associated with inversion of T_3, or when the elevated RS-T junction is coupled with an upright T_3 whose summit rises less above the level of the RS-T junction than the latter is elevated above the level of reference.

Depression of the RS-T junction in Lead I (as a reciprocal change) is significant when it measures 0.5 mm. or more; in Leads C_5 or C_6 when it measures 1.0 mm. or more; in the other chest leads when the depression us 2.0 mm. or more. A depression of the RS-T junction is more significant when associated with upright, rather than with inverted, T waves. In the diagnostic evaluation of depression of the RS-T segment, the possibility of digitalis effect must be considered.

Changes of the T Wave: Inversion of T_3 was frequently observed in the group with uncomplicated right bundle branch block; inversion of T_2 was noted only once in the absence of evidence of posterior infarction. Inverted T waves are suggestive of posterior infarction when they occur simultaneously in Leads II and III, especially when the amplitude of T_3 is more than 3.0 mm. or when progressive inversion of T_2 and T_3 is observed in serial records after an acute episode

that is clinically diagnosed as cardiac infarction. Inversion of T waves in leads from the left side of the precordium often accompanies posterior infarction with lateral extension; it may also occur, in association with significant depression of the RS-T junction, in the early stage of posterior infarction.

SUMMARY

Ninety-two patients with right bundle branch block were studied in an effort to differentiate the signs of myocardial infarction from the features of the associated right bundle branch block. Thirty-two patients presented what appeared to be uncomplicated right bundle branch block. In sixty patients the diagnosis of myocardial infarction was made (in twelve it was confirmed by post-mortem examination). Anterior infarction was diagnosed in twenty-five, posterior infarction in fifteen. The signs of anterior (lateral) and posterior infarction were combined in twenty.

Right bundle branch block has these features in common with anterior infarction: (1) Q waves in Lead I (and II) and in precordial leads from the left side, exceptionally also in precordial leads from right side positions; (2) marked elevation of the RS-T junction (up to 4.0 mm.) which may occur in some chest leads; (3) inversion of T waves in leads from the right side of the precordium.

The following features may be considered as suggestive of anterior (lateral) infarction superimposed on right bundle branch block:

1. Significant Q waves in Lead I and in the chest leads. These are Q waves which have an amplitude of one-fourth or more of the size of the R waves in the same lead, a duration of 0.04 second or more, and which show conspicuous slurring or notching; or Q waves of any size which appear in leads presenting the right ventricular pattern and are followed by late R deflections.

2. Q-wave equivalents in the chest leads. In leads from the right side of the precordium, these are deep S waves associated with low R deflections, when the amplitude of the R wave is 0.5 mm. or less and the ratio of amplitude S/R is ten or more; in leads from the left side of the precordium, deep S waves are significant when they are preceded by low R deflections whose amplitude is 3.0 mm. or less.

3. A QRS pattern characterized by low voltage of QRS in Lead I and deep S waves in Leads II and III ($r_1 S_2 S_3$). This pattern was observed in 20 per cent of the patients presenting anterior (lateral) infarction either alone or combined with posterior infarction. Early mortality in these patients was 33 per cent. The pattern $r_1 S_2 S_3$ was not observed with uncomplicated right bundle branch block and should arose suspicion of anterior wall infarction.

4. A QRS pattern with prominent negative deflections in all limb leads ($S_1 S_2 S_3$). This pattern was present in one of thirty-two patients presenting uncomplicated right bundle branch block, and in seven of forty-five in whom right bundle branch block was complicated by anterior infarction, either alone or combined with posterior infarction. Early mortality in the patients with infarction who showed this pattern was 57 per cent. Three of the patients with infarction presenting this pattern showed, in addition, low voltage of the QRS complexes

in the limb leads. All of them died shortly after the onset of cardiac infarction. Post-mortem examination was done in two of these subjects and revealed extensive myocardial infarction.

5. A straight or upward convex RS-T segment (first limb of the T wave) in association with an upright T wave, in Lead I or in leads from the left side of the precordium.

6. Significant elevation of the RS-T junction; in Lead I, an elevation which measures more than 1.0 mm.; in Lead I or in the chest leads, an elevation which is 1.0 mm. or more, and is associated with an inverted or flat T wave or with an upright T wave, whose summit rises less above the level of the RS-T junction than the distance of the latter from the level of reference.

7. Significant depression (reciprocal deviation) of the RS-T junction in Lead III, measuring more than 1.0 millimeter.

8. Significant changes of T waves; these are upright, low T waves in Lead I or in precordial leads from the left side, whose amplitude is less than 1.0 mm.; diphasic (±) or "coronary T waves" in Lead I or in the precordial leads; inverted T waves in Lead I or in the precordial leads from the left side; inverted T waves in precordial leads from the right side, which have an amplitude of 10.0 mm. or more, or an elevation of the RS-T junction measuring more than 1.0 mm.; and, finally, upright T waves in Lead III with an amplitude of more than 2.0 mm. (reciprocal change).

Right bundle branch block has these features in common with posterior infarction: (1) deep Q waves in Lead III; (2) Q waves in Lead II; (3) inverted T waves in Lead III (exceptionally also in Lead II).

The following features may be considered as suggestive of posterior infarction associated with right bundle branch block:

1. Deep Q waves or Q-wave equivalents in Lead III when they are associated with other changes suggestive of posterior infarction. Instead of the Q waves there may be QS deflections in Lead III or a W-shaped QRS_3, whose R deflection does not exceed the size of the initial downstroke. The significance of a Q_3 is enhanced when it is conspicuously slurred or notched and has a duration of 0.04 second or more.

2. A Q_2 whose amplitude is at least one-quarter the size of the following R wave (or a Q-wave equivalent in Lead II) in association with a deep Q wave (or Q-wave equivalent) in Lead III. The diagnostic significance of Q_2 increases with the ratio of amplitude Q_2/R_2. Posterior infarction is most likely to be present when the amplitude of Q_2 is more than one-half the size of R_2. Supplementary diagnostic features are: increased duration of Q_2 (0.04 second or more) and slurring or notching of the Q wave. A Q_2 equivalent may be suspected when Lead II shows an RS pattern, the R wave measuring 0.5 mm. or less in amplitude, and the ratio of amplitude S/R is ten or more.

3. An upward bow of the RS-T segment (first limb of the T wave) in association with upright T waves in Leads II and III.

4. Elevation of the RS-T junction in Lead III (and II), measuring 1.0 mm. or more, especially when it occurs in conjunction with an inverted or flat T wave or with an upright T wave, whose summit rises less above the level of the RS-T junction than the distance of the latter from the level of reference.

5. Depression of the RS-T junction in Lead I (as a reciprocal change), measuring 0.5 mm. or more; in Leads C_5 and C_6, a depression of the RS-T junction measuring 1.0 mm. or more; in the other chest leads, a depression of the RS-T junction measuring 2.0 mm. or more.

6. Inversion of T_2 and T_3, especially when the amplitude of the inverted T_3 measures more than 3.0 millimeters.

7. Inverted or diphasic ($\mp$) T waves in leads from the left side of the precordium, in association with depressed RS-T junctions.

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EFFECTS OF EMETINE HYDROCHLORIDE ON THE ELECTROCARDIOGRAM IN MAN

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THE toxic action of emetine hydrochloride on the cardiovascular system has been known for years, principally on the basis of pharmacological studies in animals. In man, however, the actual toxicity of average doses of emetine and the necessary clinical safeguards for its use in the treatment of amebic dysentery remain controversial points

Podwyssotzki,[1] in 1879, observed irregular heart action after injecting 5 to 10 mg. of emetine subcutaneously in frogs. The irregularity terminated in diastolic standstill in one hour. The arrhythmia was not classified. Although Wild,[2] in 1895, concluded that it was doubtful whether emetine would directly affect the heart in man, he advised caution in giving large doses of emetine on the basis of experiments in which diastolic arrest of the isolated frog heart was produced by perfusion of 1:20,000 solution of emetine. In 1916, Levy and Rowntree[3] investigated the effect of emetine hydrochloride on animals. They demonstrated that there was a wide difference in the toxic dose in various animals and a significant variation in toxicity of emetine preparations from different pharmaceutical manufacturers, as well as among different lots of the drug from the same firm.

In dogs, a total dosage of 3 mg. per kilogram of the most toxic preparation, given subcutaneously, killed within three days; whereas 19 mg. per kilogram of another commercial preparation required eleven days. In cats 14 mg. per kilogram (total dosage) of one preparation caused death in three days, whereas 29 mg. per kilogram of another killed only after seven days. Since Levy and Rowntree[3] reported electrocardiographic and kymographic evidence of ventricular fibrillation following intravenous injections of emetine in animals there have been numerous reports of the toxic effects of emetine on the heart.

Levy and Rowntree's[3] case report describes the first death attributed to emetine (Table I). Sayid[4] reported two cases of auricular fibrillation after emetine was administered subcutaneously. That emetine was the causative agent is doubtful in one of the reported cases since the patient had had rheumatic fever complicated by endocarditis a year previously. The patient developed auricular fibrillation two days after receiving emetine. The other patient was a 50-year-old man who developed auricular fibrillation after receiving 12 grains

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of emetine hydrochloride and 6 mg. of strychnine in twenty-two days. Boyd and Scherf[5] observed intraventricular conduction defects, inversion of T waves, and cardiac arrhythmias in experimental intoxication with emetine hydrochloride, given intravenously, in cats. The largest dose of the drug from which the cats regularly recovered was 37 mg. per kilogram of body weight. By contrast the average clinical dose of the drug in human patients is one grain subcutaneously per day (for 7 to 10 days) which would approximate a dose of 1 mg. per kilogram body weight per day in adults of average weight. Dack and Moloshok[6] recently reported a series of nine patients who were considered to have had toxic cardiac effects due to emetine therapy for amebic dysentery on the basis of the presence of electrocardiographic abnormalities. However, there was no mention of control electrocardiograms in any of these patients, and only four of the nine had electrocardiograms during the course of therapy. Electrocardiograms remained abnormal for from 4 to 8 weeks in five of the nine patients, and follow-up was not obtained in the other four instances. The regimen recommended by Dack and Moloshok is as follows: 1) The patient should be maintained on absolute bed rest in bed throughout the course of treatment. 2) The pulse rate should be recorded at frequent intervals daily and preferably graphed on the clinical record. 3) The patient should be examined and questioned at least daily for the detection of signs of toxicity such as diarrhea, fatigue, dyspnea on exertion, muscular tremors or weakness, and dizziness. 4) It is advised that an electrocardiogram be taken before treatment is instituted and after the fifth grain. Another electrocardiogram should be obtained at the completion of the course of treatment and again one week later. Use of the drug should be promptly discontinued if significant changes are found. 5) In the majority of patients with amebic dysentery as great a therapeutic effect has resulted from the administration of 5 to 7 grains (0.32 to 0.45 Gm.) of emetine hydrochloride as has been obtained with the higher doses somestimes recommended. 6) If clinical evidence of amebiasis persists after the first course of treatment and no evidence of toxicity of emetine hydrochloride has been observed, a rest period of at least a month should intervene prior to resumption of treatment. If significant electrocardiographic changes or other clinical evidence of toxicity is observed during or after the first course of treatment with emetine hydrochloride, at least two months should be allowed to intervene before further emetine hydrochloride is administered. If that becomes necessary, electrocardiographic tracings should be made after the third grain is given. It would seem safer to resort to other forms of treatment for this group of patients. 7) Emetine hydrochloride should not be used in the presence of suspected organic heart disease and should be used with great caution in patients who are anemic and debilitated.

Despite recent favorable reports on the use of chloroquine,[7,8,9] para-aminobenzoic acid,[10] bacitracin,[11] and aureomycin[12] in the treatment of amebic infections, emetine hydrochloride remains an important therapeutic agent, and it is felt that the recognition and management of potential emetine toxicity has been overemphasized recently. In large doses emetine is undoubtedly a protoplasmic poison, but if emetine is administered subcutaneously or intramuscularly in a dose of one grain daily for from 7 to 10 days there seems little likelihood of toxicity.

The fact that transient electrocardiographic abnormalities are produced by emetine is not considered an adequate reason for restricting the use of this valuable drug, any more than would similar changes from the clinical use of digitalis or quinidine contraindicate the use of those drugs in the treatment of heart disease. In fact Heilig and Visveswar[13] found that 78 per cent of their patients showed electrocardiographic evidence of improvement (increased T wave voltage) following emetine therapy, although the most likely explanation of such changes was the eradication of infection and improvement of nutrition.

A number of physicians have been concerned with the possibility that emetine might be discarded as a therapeutic agent because of fear of toxicity. Brown[14] was one of the first to emphasize the relative safety of emetine hydrochloride in the treatment of amebic dysentery, and he reported no significant cardiovascular reactions in 554 emetine-treated patients. He found no authentic report of myocardial damage in any adult receiving a total of 0.65 Gm. or less of emetine.

Cottrell and Hayward[15] saw no clinical evidence of myocardial insufficiency in 250 emetine-treated subjects. Diminution or inversion of the T wave occurred in one or more leads in twenty-five out of thirty-two patients receiving emetine, and in twelve patients there was an increase in the P-R interval amounting to 0.02-0.04 second. The electrocardiograms returned to normal in 8 to 12 days after completion of treatment. Hardgrove and Smith[16] reviewed seventy-two cases of amebic dysentery treated with emetine at Gorgas Hospital in the Canal Zone. Those ill with other diseases which might affect the electrocardiograms were eliminated. Thirty-eight of the series showed electrocardiographic changes, and thirty-three of these had depression of the T waves varying from slight lowering of the amplitude to complete inversion. They concluded that emetine produces minor changes in the electrocardiogram, consisting for the most part of T-wave depressions in all leads. These changes were most frequently noted in the bipolar limb leads and were temporary in nature.

Heilig and Visveswar[13] treated forty-five unselected patients with acute amebic dysentery with emetine. Fourteen were given one grain of emetine intramuscularly daily for 12 days, while the other thirty-one patients were given the same amount of emetine intravenously. In almost all of these patients electrocardiograms were taken after 1, 6, and 12 grains of emetine had been given. They concluded that 12 grains of emetine given in 1 grain doses daily by the intramuscular route had no damaging effect on the myocardium, even if there was some myocardial defect at the commencement of medication. The beneficial effect on the heart resulting from the improvement of the amebic infection and the general condition of the patient apparently offset any possible damaging effect of emetine on the heart. On the other hand, results of emetine administered intravenously confirmed the impression, based up to then on animal experiments, that by exceeding a certain emetine concentration, either in a single dose or by cumulative action, signs of a myocardial lesion could be produced. They reported that none of the forty-five patients showed any clinical evidence of a toxic reaction.

The literature has been surveyed and numerous reports of death due to emetine were found. An attempt has been made to evaluate these reports objectively

in an effort to determine if these deaths were due to the effect of emetine on the cardiovascular system. These reports are recorded in Table I.

Gimble, and his associates[17] determined the relative concentrations of emetine in the rat and dog and found the concentrations to be similar in the tissues of both the animals. It is of interest that the concentrations were of the following order: Liver > kidney > spleen > lung > brain > heart > skeletal muscle > blood. Parmer and Cottrill[18] found relatively low concentrations of emetine in the heart muscle and skeletal muscle of rabbits after a single injection of emetine. Although the concentration is low in skeletal muscle and heart muscle as compared to other tissues, the effects noted in man are mainly those of skeletal muscle and heart muscle. Since emetine is now being used on a considerable scale not only in the treatment of amebiasis, but also in the conditioned reflex treatment of chronic alcoholism, the determination of its actual toxicity and the necessary clinical safeguards are most important. Melchior[19] of Turkey, even reports treating "malignant furuncles" with emetine. Albright and Gordon[20] feel that emetine should be used in the treatment of all forms of amebiasis regardless of the phase of symptomatology.

MATERIAL AND METHODS

From March, 1947, to July, 1949, there were forty-one patients treated with emetine at the Veterans Administration Hospital, Jefferson Barracks, Missouri. Fifteen patients did not have adequate electrocardiographic observations and therefore cannot be evaluated; these patients had only one or two electrocardiograms, obtained at unsuitable times in relationship to their emetine treatment. Of the remaining twenty-six patients, twenty-five were men (twenty-one white, four Negro) with only one white female patient. The usual indication for emetine therapy was some form of amebiasis (twenty-two patients). Four patients received a therapeutic trial of emetine. The patients' average age was 35 years with a range from 21 to 59 years.

One grain (0.065 Gm.) of emetine hydrochloride was administered daily by the intramuscular route in twenty-one patients while in five it was given subcutaneously. In twelve patients emetine was given in divided doses of a half grain twice a day. The total dose per course varied from 3 to 10 grains; sixteen patients received only one course, seven patients received two courses and three patients received three courses. Treatment of those patients receiving more than one series of injections was interrupted by short rest periods. The rest period ranged from nine to forty-six days, averaging twenty-three days. In nineteen patients it was possible to obtain electrocardiograms prior to, during, and following treatment with emetine. Many of the patients were followed electrocardiographically until all signs of emetine effect had subsided, but it was not possible to do so in all. The observations on the duration of toxicity are, therefore, incomplete in some instances. The conventional limb leads and precordial leads V_2, V_4 and V_6 were recorded on a Sanborn Viso-Cardiette except in a few instances where a Simpli-Trol Portable Model Cambridge Electrocardiograph was used. CF leads were used prior to October, 1947, after which time precordial V leads were obtained.

TABLE I. EVALUATION OF REPORTS OF DEATH ATTRIBUTED TO EMETINE

CASE NO.	AUTHOR	DOSAGE	SIGNS AND SYMPTOMS	AUTOPSY	REMARKS
1	Levy and Rowntree[1]	Total of 29 grains subcutaneously in 20 days	Age 56; weight 69.5 kilograms; muscular weakness; no amebae found; evidence of acute renal insufficiency with azotemia; vasomotor collapse.	Diffuse bronchopneumonia; syphilitic aortitis; dilatation of the heart, chronic passive congestion of viscera.	Dose too high; renal death (?)
2	Johnson, H. H., and Murphy, J. A.: Mil. Surgeon **40**:58, 1917	Total of 25 grains in 54 days	Age 22; amebic dysentery; difficulty swallowing; irregular pulse, tachycardia, evidence of congestion at lung bases, temperature 103°.	Autopsy 1 hour post-mortem; heart negative; pneumonia, lobar atypical (diplococci, no amebae), septic bronchitis.	Dose too high; not cardiac death
3	Johnson, H. H., and Murphy, J. A.: Mil. Surgeon **40**:58, 1917	Total of 23.5 grains in 35 days	Age 38; (chronic recurrent amebic dysentery); nervousness and weakness; food regurgitation, irregular rhythm, temperature 98.4°, pulse rate 128 to 140.	Heart enlarged, right ventricle flaccid "like gelatine," myocardium as thin as 1 mm. in places, replacement with fat (6-14 mm.); left ventricle thickened (2½ cm.); pneumonia atypical, lobar.	Dose too high; cardiac disease probably present prior to treatment because of thickness of myocardium
4	Soca, E.: Bull. et mém. Soc. méd. d. hôp de Paris **46**:768, 1922	Total of 16.2 grains in 18 days	Age 37; muscular weakness, painful arms and legs; tachycardia, neuritis; bulbar symptoms.	None	No indication of a cardiac death
5	Bais, W. J.: Abstr. Trop. Dis. Bull. **20**:63, 1923.	Total of 16.2 grains in 6 weeks	Muscular weakness, tachycardia beginning 2 days after last injection.	Serious parenchymatous degeneration of heart muscle.	Information obtained from abstract
6	Stern, E.: Arch. f. Schiffs u. Tropen-Hyg. **32**:610, 1928.	0.3 grains intramuscularly	Age 2 years; began to vomit immediately after injection; pulseless, Cheyne-Stokes respiration.	None	Apparently anaphylactic shock
7	Leibig, F. J.: Am. J. M. Sc. **179**:83, 1930.	Total of 19.4 grains given intravenously and intramuscularly in a two-month period plus 9.2 Gm. ipecac	Age 21; weakness; pulse 100; mild peripheral neuritis; signs of myocarditis; respiration embarrassed; died 6 days after discontinuing emetine.	Parenchymatous degeneration of liver; acute diffuse nephritis; acute parenchymatous degeneration of adrenals; acute hyperplasia of spleen; heart grossly showed slight myocarditis.	Dose too high; cardiologist apapparently felt no cardiac involvement prior to death; microscopic examination of heart not reported
8	Kattwinkel, E. E.: New England J. Med. **240**:995, 1949.	Total of 12.5 grains intramuscularly in 11 days	Age 33, acutely ill, pulse 140, gallop rhythm; blood pressure 70/60, engorged liver and lungs; ECG—inverted T waves in all leads; in 1945 no evidence of cardiac damage.	Heart 450 grams; few dark brown petechiae; myocardium soft, flabby, light red brown; pericardium contained diffuse and focal infiltration, lymphocytes, histocytes and plasma cells; muscles showed ischemic necrosis; infiltration with histocytes; lymphocytes and rarely neutrophils; diagnosis; toxic myocarditis.	Apparent cardiac death due to emetine, in conditioned reflex treatment of chronic alcoholism.

RELATION OF ELECTROCARDIOGRAPHIC CHANGES TO DOSE

It would be necessary to take daily electrocardiograms to determine when the first electrocardiographic changes occur but unfortunately this was not possible. Tracings were obtained at varying intervals during emetine therapy and electrocardiographic changes were noted with the dose as low as two grains.

Klatskin and Friedman[21] recently reported one patient showing electrocardiographic changes after 2 grains of emetine. It is noted in Table III that the electrocardiographic changes became more marked with increasing doses of emetine. With a total dose of less than 9 grains of emetine, P wave changes were not noted.

ELECTROCARDIOGRAPHIC CHANGES

The electrocardiograms were considered normal in all but two patients prior to treatment. The outstanding findings are listed in Table III and consisted primarily of lowering and inversion of T waves and lengthening of the P-R interval. The T waves were frequently flattened or lowered in all leads recorded. Similar electrocardiographic abnormalities have been reported previously.[6,13,15,16,21,22]

DURATION OF ELECTROCARDIOGRAPHIC CHANGES

Since emetine is slowly excreted and its action is cumulative, it is not surprising that electrocardiographic changes are sometimes prolonged. Dack and Moloshok[6] reported one patient having an abnormal record for over five months. These authors reported a lag of one or two weeks in the time of the appearance of electrocardiographic abnormalities following the discontinuation of treatment in some instances.

In our series an insufficient number of electrocardiograms was taken to determine exactly when the electrocardiogram returned to normal following the discontinuance of emetine.

Sixteen of the twenty-six patients were observed over a sufficient period of time to permit evaluation. All of these patients were considered to have electrocardiographic abnormalities during or following emetine therapy, but with subsequent return to normal one to seventeen months (average nine months) after emetine therapy was terminated. Although abnormal electrocardiograms were observed in these sixteen patients following emetine, many of the forty observed had normal electrocardiograms during therapy. The patients with normal electrocardiograms during emetine treatment did not have sufficient electrocardiographic follow-up to determine whether their electrocardiograms ever became abnormal and therefore are not included. Six of the reported twenty-six patients had abnormal electrocardiograms following emetine therapy (1 to 5 days after treatment was discontinued). An adequate follow-up was not obtained to determine if and when these electrocardiograms returned to normal. There were five deaths in the forty patients treated with emetine, four of which are included in the twenty-six reported patients. Autopsies were performed in all five and in each the cause of death was considered unrelated to emetine. The

TABLE II. SUMMARY OF TWENTY-SIX PATIENTS TREATED WITH EMETINE

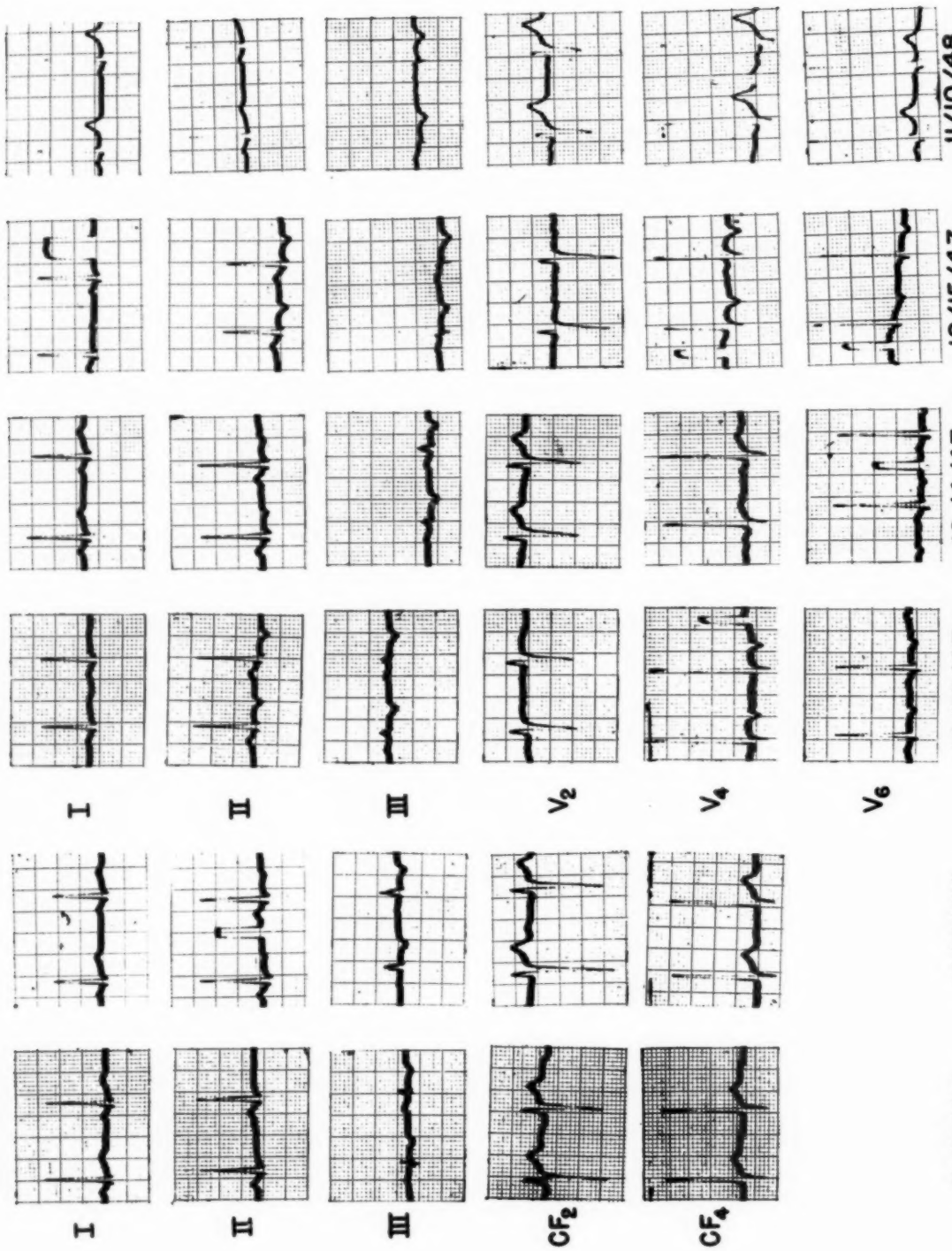
CASE NO.	SEX	AGE	WHITE OR NEGRO	TOTAL AMOUNT OF EMETINE (GR.)	NO. OF COURSES	REST (DAYS) BETWEEN COURSES	NO. OF GR. WHEN ECG CHANGES NOTED*	TIME INTERVAL AFTER EMETINE BEGAN ECG CHANGES NOTED*†
1	M	36	N	18	2	46	6	6 days
2	M	53	W	14	2	18	7	15
3	M	28	W	7	1	—	9	5
4	M	21	W	11	2	9	5	5
5	M	33	W	7	1	—	7	10
6	M	56	W	9	1	—	6	6
7	M	25	W	19	2	31	11	22
8	M	37	W	19	3	3 and 5	5	6
9	M	48	W	5	1	—	5	13
10	M	25	N	9	1	—	9	14
11	M	27	N	24	3	18 and 12	8	8
12	M	51	W	9	1	—	8	8
13	M	38	W	24	3	30 and 16	9	11
14	M	32	W	6	1	—	2	2
15	M	32	W	18	2	41	11 (3 days after 2nd course began)	7 weeks (3 days after 2nd course began)
16	M	37	W	20	2	11	4	4
17	M	28	W	6	1	—	6	7
18	M	31	N	7	1	—	7	9
19	M	25	W	8	1	—	5	5
20	F	33	W	13	2	19	7	7
21	M	32	W	7	1	—	7	5 months
22	M	29	W	7	1	—	3	3
23	M	59	W	7	1	—	7	8
24	M	33	W	5	1	—	4	4
25	M	26	W	5	1	—	5	8
26	M	53	W	9	1	—	9	10

*Electrocardiograms were not obtained daily and therefore electrocardiographic changes may have occurred earlier.
†Numerals in this column, except those otherwise labeled, indicate days.

TABLE III. ELECTROCARDIOGRAPHIC CHANGES OBSERVED IN TWENTY-SIX PATIENTS RECEIVING EMETINE

TABLE III. ELECTROCARDIOGRAPHIC CHANGES OBSERVED IN TWENTY-SIX PATIENTS RECEIVING EMETINE

NO.	TOTAL GRAINS OF EMETINE	ELECTROCARDIOGRAPHIC CHANGES	RETURNED TO NORMAL	COMMENT
1	18	Lengthening of P-R interval; T waves lower in Leads I and V_2; T waves inverted in II, V_4 and V_6	Yes	Last ECG normal 13 months after emetine therapy.
2	14	Lower T waves in I, II, III, V_4 and V_6	Yes	Last ECG normal 9 months after emetine therapy.
3	7	Lower T waves in I, II, V_2 and V_6; T waves in III inverted	Yes	Last ECG normal 6 months after emetine therapy.
4	11	Lower T waves in I, II, III, V_2, V_4 and V_6	——	Last ECG 3 days after emetine discontinued.
5	7	Lower T waves in II, III, V_4 and V_6	Dead	Died 7 months after therapy; diagnosis chronic ulcerative colitis, pelvic abscess; ECG abnormal 1 month after emetine therapy.
6	9	Lower T waves in I, II, V_2, V_4 and V_6	Yes	Last ECG normal 10 months after emetine therapy.
7	19	Lower T waves in I, II, III, V_2, V_4 and V_6	Yes	Last ECG normal 5 months after emetine therapy.
8	19	Lower T waves in I, II, III, V_2, V_4 and V_6	Yes	Last ECG normal 3 months after emetine therapy.
9	5	Lower T waves in I, II and III; inverted T waves in CF_2 and CF_4, isoelectric T waves in CF_6	Dead	Died 2 months after treatment; diagnosis—hepatoma with generalized carcinomatosis; last ECG abnormal 8 days after therapy.
10	9	Lengthening of P-R interval; lower T waves in I, II, III, V_2, V_4 and V_6	——	Last ECG abnormal 6 days after emetine therapy.
11	24	Lower T waves in I, II and III; inverted T waves in CF_2 and CF_4	Dead	Died 2 weeks after therapy; diagnosis—generalized peritonitis, intra-abdominal abscess; last ECG abnormal last day of therapy.
12	9	Lower T waves in I and V_6	Dead	Died 6 days after therapy; diagnosis—myocardial infarction; ECG abnormal prior to therapy.
13	24	Lower P waves in I, II and III; lower T waves in I, II, III, CF_2 and CF_4	Yes	Last ECG normal 16 months after emetine therapy.
14	6	Lower T waves in I and II; inverted T waves in III; diphasic T waves in V_4 and V_6	Yes	Last ECG normal 9 months after emetine therapy.
15	18	Lower P waves in II; lengthening of P-R interval; lower T waves in I, II and III	Yes	Last ECG normal 14 months after emetine therapy.
16	20	Lower T waves in I, II, III, V_4 and V_6	——	Last ECG 1 day after emetine therapy.
17	6	Lower T waves in I, II, III, V_2, V_4 and V_6	Yes	Last ECG normal 17 months after therapy.
18	7	Lower T waves in II and V_6	Yes	Last ECG normal 9 months after therapy.
19	8	Lower T waves in I, II, V_4 and V_6	——	Last ECG 1 day after emetine was discontinued.
20	13	Lower P waves in I, II and III; lower T waves in I, II, V_2, V_4 and V_6; inverted T waves in III	——	Last ECG 3 days after emetine was discontinued.
21	7	Lower T waves in II and III	Yes	Last ECG normal 12 months after emetine therapy.
22	7	Lower T waves in I, II and III	Yes	Lase ECG normal 14 months after emetine therapy.
23	7	Lower T waves in V_4	Yes	Last ECG normal 6 months after emetine therapy.
24	5	Lower T waves in I, II, III, V_2 and V_4	——	Last ECG 5 days after therapy.
25	5	Lower T waves in I, II, V_2, V_4 and V_6	Yes	Last ECG normal 1½ months after emetine therapy.
26	9	Lower T waves in I, II, V_2 and V_4; inverted V_6	——	One month after emetine therapy ECG was similar to pre-emetine ECG.


I
II
III
V2
V4
V6
11/10/48
12/15/47
12/4/47
10/16/47
I
II
III
CF2
CF4
10/9/47
10/2/47

causes of death are listed in Table III. Histopathologic sections of the heart taken at the junction of the posterior leaflet of the mitral valve and the left ventricle were studied carefully in each autopsy but no evidence of myocarditis was noted.

TABLE IV. ELECTROCARDIOGRAPHIC CHANGES IN TWENTY-SIX PATIENTS FOLLOWING EMETINE TREATMENT

CHANGES	NUMBER OF CASES
1) Lower P Waves	
Lead I	2
Lead II	3
Lead III	2
2) Lengthening of P-R Interval	3
3) T Wave Changes in Bipolar Limb Leads	
Lower T waves in I	23
Lower T waves in II	23
Lower T waves in III	16
Inverted T waves in I	0
Inverted T waves in II	1
Inverted T waves in III	3
4) T Wave Changes In Precordial Leads	
T lower in CF_2	1
T lower in CF_4	1
T lower in CF_6	1
T inverted in CF_2	2
T inverted in CF_4	2
T lower in V_2	11
T lower in V_4	15
T lower in V_6	17
T inverted in V_2	0
T inverted in V_4	1
T inverted in V_6	6

SUMMARY AND DISCUSSION

Forty-one patients were treated with emetine hydrochloride. Fifteen patients had only one or two electrocardiograms obtained at unsuitable times in relationship to their emetine therapy and therefore cannot be evaluated. Electrocardiograms were obtained before, during and after emetine treatment in nineteen of the remaining twenty-six patients.

Electrocardiographic changes were noted in twenty-six patients. One patient had electrocardiographic changes after 2 grains of emetine. The electrocardiographic changes became more marked with increasing doses of emetine. Below a total dosage of 9 grains of emetine, P wave changes were not noted. The outstanding electrocardiographic changes due to emetine hydrochloride consisted of lowering and inversion of T waves and lengthening of the P-R interval. The T waves were frequently flattened or lowered in all leads recorded. The fact that there may be a lag of one to two weeks before electrocardiographic changes appear has been reported by Dack and Moloshok.[6] This lag was not

observed in any of our patients. Sixteen patients were observed one to seventeen months after emetine therapy was discontinued and were found to have normal electrocardiograms.

We have had no severe toxic reactions attributed to emetine hydrochloride. There were five deaths in the forty-one observed patients. No evidence of toxic myocarditis was noted at autopsy in these five patients.

The literature was reviewed and the cardiovascular deaths attributed to emetine were critically analyzed (Table I).

Dack and Moloshok[6] recommended that the patient should be maintained on absolute bed rest throughout the course of emetine treatment. It has been our policy to allow all patients receiving emetine bath room privileges, restricting their activity to their hospital room but not enforcing strict bed rest unless the patient's general condition made this desirable. There has been no definite evidence presented that exercise is detrimental to these patients despite the advocacy of bed rest by almost all writers on this subject. This problem may be as difficult of ultimate solution as the similar problem of bed rest in the treatment of rheumatic fever. Certainly insistence on bed rest during emetine therapy in patients not ill enough to require bed rest for the presenting illness may have adverse psychological effects on the patient, as may the daily leading question regarding possible toxic signs. Whether emetine should be used in patients having heart disease is also disputed by many writers.[6,11,21] Although granting that the evidence is inconclusive, Klatskin and Friedman,[21] believe that there is probably an added risk in using emetine in the presence of organic heart disease. They conclude that the decision to use emetine in the presence of organic heart disease must rest on the urgency of the indications for emetine. A rest period of one month before repetition of a course of emetine is considered adequate to permit excretion or destruction of the previously administered emetine. In some cases a shorter rest period has been necessary due to the urgent need for emetine treatment.

CONCLUSIONS

1. Electrocardiographic changes of some degree were observed in all of twenty-six carefully studied emetine treated patients.

2. Despite the high incidence of electrocardiographic changes in emetine therapy no evidence of permanent cardiac damage was found.

3. Emetine hydrochloride remains an important therapeutic agent and it is felt that means of detection of emetine toxicity have recently been made too rigid. In large doses, emetine is undoubtedly a protoplasmic poison but if emetine is administered subcutaneously or intramuscularly in a dose of 1 grain daily for 7 to 10 days there seems little likelihood of toxicity.

4. The fact that transient electrocardiographic abnormalities are produced by emetine is not considered an adequate reason for restricting the use of this valuable drug, any more than would similar changes from the clinical use of digitalis or quinidine contracindicate the use of those drugs in the treatment of heart disease.

5. The necessity for bed rest during emetine therapy is considered unproven.

6. On the basis of a survey of previously reported fatal and non-fatal emetine reactions, there seems to be little likelihood of significant toxic reaction if emetine is administered subcutaneously or intramuscularly in a dose of 1 grain daily for 7 to 10 days.

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THE UNIPOLAR ELECTROCARDIOGRAM OF THE NEWBORN INFANT

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THIS report describes the electrocardiographic pattern in the normal infant in terms of the unipolar method. The infant record has been described by many investigators, but usually in terms of the standard leads. Groedel and his co-workers[1,2] have described the precordial pattern in infants using CR leads and in terms of the dextro- and levocardiograms. Battro and Mendy[3] studied thirteen children from 0 to 2 years of age with the unipolar precordial leads V_1 to V_6. They did not take unipolar limb leads or right chest leads. As will be shown later, the lack of these two types of leads prevented the demonstration of a definite and consistent pattern.

Cardiac problems in infancy are usually those of congenital heart disease and arrhythmias. For their solution we can expect the electrocardiogram to give evidence of the conduction mechanism, of hypertrophy of the auricles, and of abnormal ventricular preponderance. When similar problems have arisen in the adult, we have found that the unipolar method has often been able to supply the needed information more clearly than the standard leads.

TECHNIQUE

The records were taken with a Sanborn Viso-Cardiette, the electrodes were of the infant type that are commercially available. The infants were not restrained in any way, they were kept quiet by offering a bottle of water. Four infants could thus be examined in an hour. The infants were examined by us to rule out any abnormality that might affect the heart.

The following leads were taken: the three standards leads, the augmented unipolar limb leads, V_{6R} (right lateral chest), V_{4R} (right anterior chest), V_{sternum}, V_4 and V_6.

This report is based on the examination of fifty infants 1 to 6 days old.

FINDINGS

Figure 1 shows six representative electrocardiograms; each line constitutes the complete record of an infant.

From the service of Julius Burstein, M.D., Department of Electrocardiography, and from the service of Louis H. Barenberg, M.D., Department of Pediatrics, Morrisania City Hospital.

The P wave was always inverted in Lead aV_R, always upright in aV_F, V sternum, V_4, and V_6. In the other leads P was usually small, either upright or inverted. In V sternum, P was most prominent, usually peaked, and never more than 2.5 mv. high.

The QRS complex always showed a predominantly upright complex in V_{6R} and a downward complex in aV_L. The other leads varied considerably.

S-T deviations were seen quite often, usually depressions in V_{4R}, V sternum, and V_4.

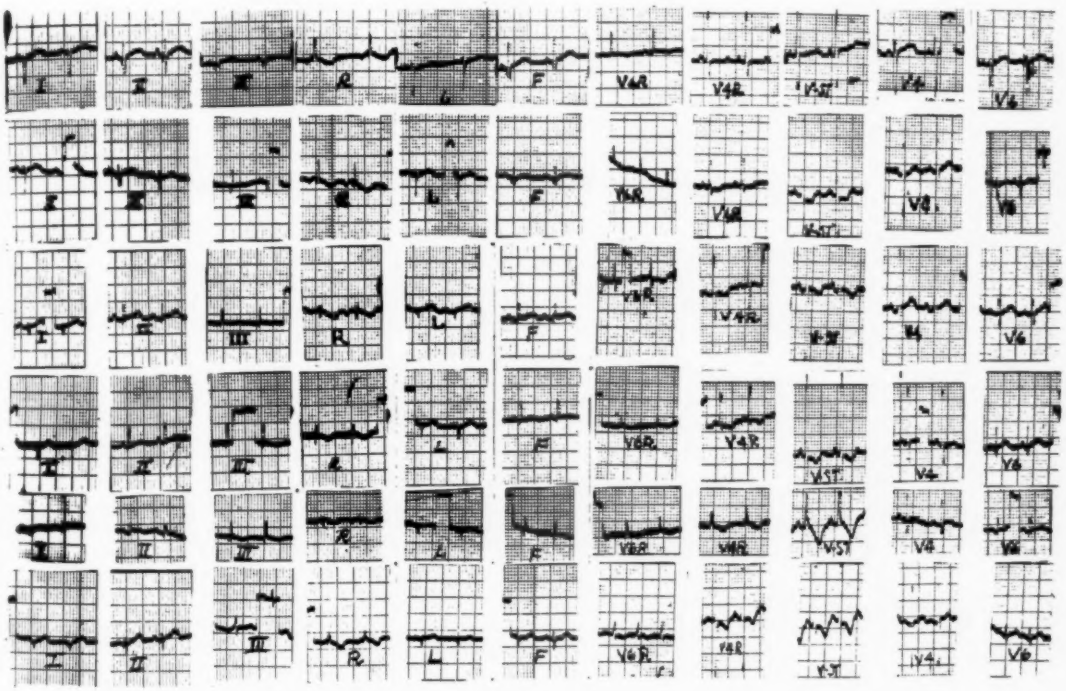

Fig. 1.—Electrocardiograms of six normal infants. The main deflection is always down in aV_L, always up in V_{6R} and variable in V_6.

The T wave was generally inverted in leads from the right side and upright in leads from the left. During the first 48 hours of life the T wave in aV_L was often distinctly inverted, later the T wave was always upright in aV_L. No record showed a definitely upright T wave in aV_R or V_{6R}, or a definitely inverted T wave in V_6. The other leads showed striking ST-T waves (Fig. 1, B, C, D, and E). Because they were so frequent in apparently normal infants, they must be considered as normal. At present infant electrocardiographic problems are little influenced by ST-T changes. This is fortunate, because in these subjects one should be conservative in judging ST-T forms as abnormal.

In one apparently normal infant we found what appears to be a right bundle branch block with a QRS of .08 second (Fig. 2). The occurrence of right bundle branch block in normal infants is unusual but has been noted by others.[4]

DISCUSSION

The normal QRS pattern of the newborn infant consists of a main deflection that is upright in V_{6R} and downward in aV_L. This pattern may be due to the position of the infant heart or to the relative right ventricular preponderance that is anatomically present.[5,6] Both factors probably contribute to this pattern. It should be emphasized that, contrary to the adult record, V_6 cannot be considered as the left component of the electrocardiogram. Figure 1 shows the wide variations of the normal QRS pattern in V_6 which make this lead unsuitable for determining ventricular preponderance.

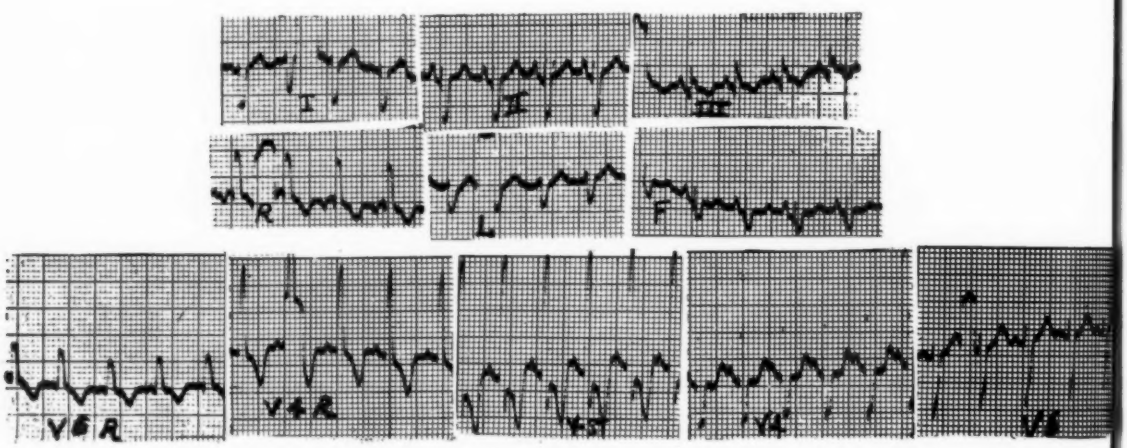

Fig. 2.—Tracing of a normal newborn baby. The QRS is 0.08 second. Pattern is similar to right bundle branch block.

The ST-T pattern is in general similar to that of the adult, except that the middle precordial leads (V_{4R}, $V_{sternum}$, and V_4) normally show striking forms. The cause of this is obscure.

Myers, Klein, and Stofer[7] often found it necessary to take a lead to the right of V_1 in order to establish the presence of an upright QRS on the right side in patients with right ventricular preponderance. As our experience with unipolar leads increased, we also found it informative to go beyond the V_1 to V_6 positions. By taking unipolar leads from the limbs and from the right lateral chest wall across to the left, we have been able to find a distinctive pattern that seems to be valid normally for all these subjects. The scope of the exploration seems to be wide enough to encompass all the variations in electrical positions encountered in normal subjects. Therefore a deviation from the normal should be significant clinically.

SUMMARY

1. Fifty normal infants in the first week of life were examined with the unipolar method.

2. The leads recommended are: the augmented unipolar limb leads, V_{6R}, V_{4R}, V sternum, V_4, and V_6.

3. The P wave was always inverted in aV_R, and always upright in aV_F, V sternum, V_4, and V_6. P was never more than 2.5 mm. high in V sternum.

4. The T wave was as a general rule inverted in leads from the right chest wall and upright in leads from the left chest wall.

The QRS complex showed a very definite and clinically significant pattern. Every tracing showed an upright complex in V_{6R} and a downward complex in aV_L.

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THE EFFECT OF INCREASED VENOUS RETURN ON THE VENOUS PRESSURE IN PATIENTS WITH CONGESTIVE HEART FAILURE

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VENOUS return to the right auricle and the level of venous pressure have been believed to play an important role in the physiology of the circulation since Starling carried out his classic experiments.[1] Not only has this factor been considered of great importance in regulating cardiac output, but elevation of peripheral venous pressure is an integral part of the picture of congestive failure of the right side of the heart, according to the "backward failure" hypothesis. Both of these concepts have been challenged, and it has been held by some that when the peripheral venous pressure is elevated it is mainly due either to increase in circulating blood volume or to increase in venous tone.

The majority of studies of the venous pressure in human beings have dealt with observations carried out in the resting state. These have a limited value, and it is of importance to study the response of the circulation, including the venous pressure, under conditions of stress, for it is under such conditions that signs of congestive failure first develop. The recognition of the importance of such stress has led to the suggestion of the measurement of venous pressure during various maneuvers as tests of cardiac competence.[2-8] Such maneuvers are exercise, administration of intravenous fluids, abdominal compression, and passive elevation of the legs. It has been reported that in individuals with competent circulations no elevation of venous pressure will result from such procedures, whereas patients with failure of the right side of the heart will respond with an increase.

These tests have also been employed as a means of studying the pathogenesis of cardiac failure. An illustration of this is the report of Landis and co-workers,[9] who found that after coronary ligation in dogs venous pressure became elevated only during exercise or when intravenous infusions were given.

The present report is concerned with a study of the venous pressure in patients with different types of congestive heart failure, and with the effects of the maneuvers described above.

METHODS

All subjects were studied after resting for 15 minutes. Venous pressures were determined in a prominent vein at the elbow using a phlebomanometer as

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originally described by Burch and Winsor,[10] equipped with a wash-out system so that a slow drip of heparinized saline could be infused between readings. At no time was more than a total of 50 c.c. of fluid admitted per hour through this system. The needles, glass and rubber tubing as well as the manometer were coated on the inside with General Electric Drifilm[11] which prevented clotting and greatly reduced the "drag" in the system due to capillary attraction. The apparatus was sensitive to changes of venous pressure as small as 5 mm. of saline. Right atrial pressures were recorded by optical registration with a sensitive Hamilton manometer through a cardiac catheter. Pressures were corrected to a reference point measured 5 cm. below the sternal angle of Louis.

PROCEDURES

1. Exercise was produced by having the subject push with his feet against a hinged footboard which had a horizontal stroke of 12 inches and was counterweighted in such a way that one stroke would lift 20 pounds. Exercise was timed so that the subject delivered 10 strokes with each leg in one minute which required a total of about 400 foot pounds of work. This was equivalent to walking slowly on the level and was not as strenuous as climbing a flight of stairs. Placing the foot upon the board elevated the leg only 10 degrees and usually produced no effect or only a slight, transient rise in venous pressure which was always allowed to fall to the original resting level before exercise was started.

2. Abdominal compression was produced by firm, sustained manual compression of the epigastrium for one minute. This amounted to about 15 pounds of pressure when maintained just below the level of discomfort to the subject. No difference in response was noted when pressure was made over the right upper quadrant and only insignificant differences were noted by pressure in the lower quadrants.

3. Elevation of the legs was performed by passive lifting of both legs manually and by placing the heels in a padded support in such a way that the angle produced with the trunk was about 45 degrees. This position was maintained for one minute.

The infusion of saline and human albumin and the measurement of the hematocrit were done in the usual manner.

Venous pressures were measured at intervals of fifteen seconds for five minutes before, during, and for five minutes after each maneuver. Frequently, during periods of rapid pressure change, readings were made at even more frequent intervals. During all maneuvers the subject was instructed to breath quietly and normally with his mouth open to eliminate effects due to breath holding or variations in respiration. Care had to be exercised to observe this precaution, for when the breath is held the maneuver of abdominal compression particularly becomes a modified "Valsalva" due to displacement of the diaphragm upward and abnormal elevation of venous pressure may be elicited in normal subjects. Each maneuver was repeated at least three times, and only those experiments showing consistent results were selected for this report.

RESULTS

A. *Normal subjects.*—The average resting venous pressure in eight subjects was 65 mm. with a range of from 25 mm. to 90 millimeters. Abdominal compression produced either no change in venous pressure or a slight fall up to 20 mm., which usually persisted during the period of compression and then rose quickly when the pressure was released. Exercise of the mild degree employed produced no change in pressure except in two subjects, where a slight rise of 10 mm. occurred. Passive elevation of both legs did not change the pressure (Table I).

B. *Patients with clinical failure of the right side of the heart and with chronic constrictive pericarditis.*—This group includes five patients with arteriosclerotic heart disease and four with rheumatic heart disease with mitral stenosis. One patient was studied on two successive hospital entries. All had evidence of chronic right-sided heart failure with distended neck veins, palpable livers, edema, and, frequently, fluid accumulations in the chest or abdomen. In addition three patients with chronic constrictive pericarditis are included in this group. They presented the same clinical picture of edema and venous distention as the other patients.

The average resting venous pressure was in most instances well above normal with an average of 175 mm. and a range of from 95 to 305 millimeters. Abdominal compression, with one exception, produced a prompt and prominent elevation of venous pressure lasting throughout the period of compression and usually falling quickly when pressure was removed. An average rise of 94 mm. with a range of 40 to 160 mm. was observed. The single exception was a 35-year-old woman with mitral stenosis who was 6 months pregnant (Case 9). Abdominal compression produced a prompt fall in venous pressure of 40 mm. with a prompt return to normal upon release of pressure. Her response to exercise and leg raising was similar to that of the other patients in this group. The explanation for the paradoxical drop in pressure during abdominal compression may have been that some of the placental blood flow was shut off, producing an effect similar to closing off an arteriovenous fistula and the resultant decrease in venous return was greater than any increase due to the usual mechanism during abdominal compression.

In every instance a prompt and definite rise occurred during exercise. The average rise was 64 mm. with a range of 30 to 90 millimeters. After the cessation of exercise, in most subjects the pressure fell within about 20 seconds to the resting level, but this fall was usually somewhat slower than the fall after abdominal compression. However, in one subject the fall was conspicuously prolonged to four minutes. In all subjects the magnitude of the rise occurring during exercise was somewhat less than that occurring during abdominal compression.

Passive elevation of the legs produced a prompt rise of venous pressure averaging 35 mm. with a range of from 20 to 80 millimeters. The rise and fall were usually prompt and complete in 15 seconds.

In several of these subjects the effect of prolonging the duration of the maneuver up to 5 minutes was studied. During this period the venous pressure

TABLE I. CHANGES IN PERIPHERAL VENOUS PRESSURE PRODUCED BY ABDOMINAL COMPRESSION, LIGHT EXERCISE, AND PASSIVE LEG RAISING, IN NORMAL SUBJECTS AND PATIENTS WITH HEART FAILURE

CASE NUMBER	VENOUS PRESSURE (MM. OF SALINE)				REMARKS*
	RESTING LEVEL	CHANGE WITH ABDOMINAL COMPRESSION	CHANGE WITH EXERCISE	CHANGE WITH LEG RAISING	
		NORMAL SUBJECTS			
1	75	0	0	0	
2	25	−20	+10	0	
3	55	0	0	0	
4	80	0	0	0	
5	90	−10	+10	0	
6	75	−20	0	0	
7	80	−20	0	0	
8	40	−10	0	0	
		PATIENTS WITH RIGHT-SIDED HEART FAILURE			
9	95	−40	+70	+50	RHD, MS, 6 months pregnant
10	130	+50	+50	+30	RHD, MS
	170	+70	+30	+20	
11	260	+120	+50	+20	RHD, MS
12	305	+90	+80	+20	RHD, MS
13	120	+70	+50	+20	ASHD
14	120	+90	+60	+25	ASHD
15	145	+120	+70	+40	ASHD
16	150	+40	+60	+50	ASHD
17	240	+140	+80	+50	ASHD
		PATIENTS WITH CHRONIC CONSTRICTIVE PERICARDITIS			
18	115	+80	+50	+30	
19	130	+100	+90	+80	
20	290	+160	+90	+30	
		PATIENTS WITH PURE LEFT-SIDED HEART FAILURE			
21	30	0	0	0	ASHD
22	40	0	0	0	ASHD
23	60	0	+10	0	ASHD
24	70	0	+10	0	ASHD
25	85	−20	0	0	RHD, MS
26	25	+10 to −10	+30	0	RHD, MS
27	65	+15 to 0	+20	0	RHD, MS
28	70	+20 to −20	0	0	RHD, MS
29	60	+30 to 0	+30	+10	RHD, AS
30	70	−30	+30	0	RHD, AS

*RHD, rheumatic heart disease; MS, mitral stenosis; AS, aortic stenosis; ASHD, arteriosclerotic heart disease.

usually showed no tendency to fall but maintained its high level until the maneuver was interrupted, after which the pressure fell in the usual manner.

The alteration of venous pressure responses occurring in progressive congestive failure is illustrated in Figure 1. The patient had arteriosclerotic heart disease with right- and left-sided heart failure. In spite of digitalis, salt restriction, and weekly injections of Salyrgan, his congestive failure became progressively more severe, requiring repeated hospital admissions over a period of three months. The degree of weight gain is indicated in the figure. Not only is the magnitude of each response greater than before, but the venous pressure fall after cessation of exercise is prolonged in the second study. This type of exercise response has been described previously by Szekely.[4]

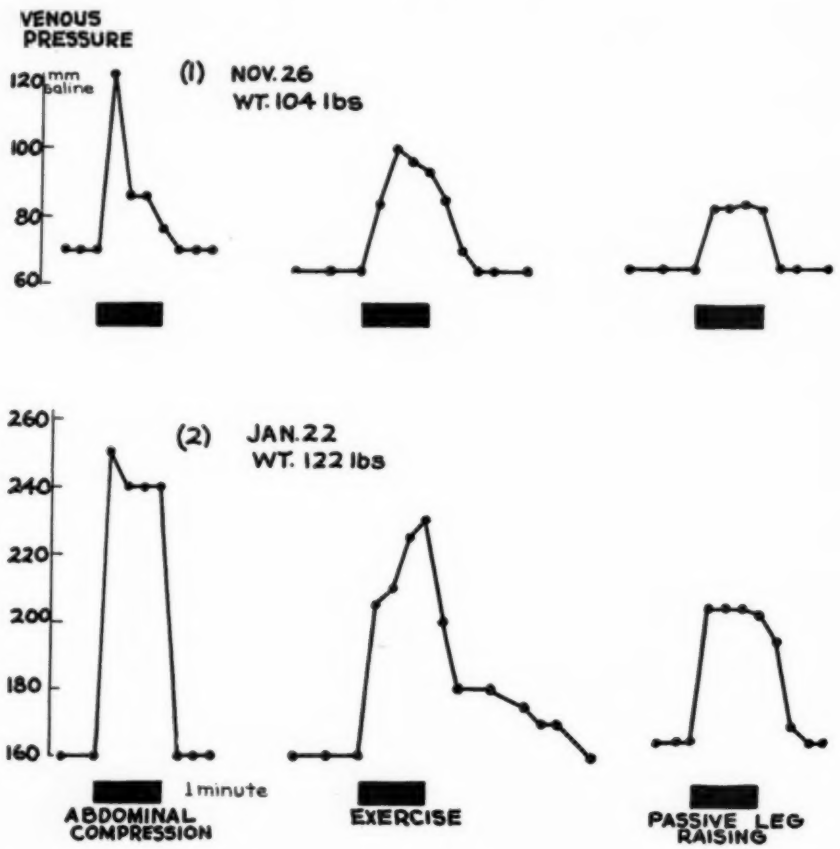


Fig. 1.—The venous pressure responses to abdominal compression, exercise and passive leg raising in a patient with progressive congestive heart failure.

Figure 2 illustrates the progressive improvement in the venous pressure responses in another patient in whom the signs of heart failure diminished under therapy with digitalis and diuretics. It is interesting to note that after 13 pounds of weight loss the venous pressure responses were reduced but still ab-

normal. Intravenous saline elevated the resting level of venous pressure but did not change the magnitude of the responses. After further weight loss the pressure responses were normal and intravenous saline actually produced a slight fall in venous pressure.

C. *Patients with pulmonary congestion but no evidence of right-sided heart failure.*—Each patient in this group had severe dyspnea on effort with râles at the lung bases and x-ray evidence of pulmonary congestion. None of these patients, however, had any evidence of right-sided heart failure in the form of hepatic enlargement, edema or fluid accumulations in the chest or abdomen. Their resting venous pressures were normal (Table I).

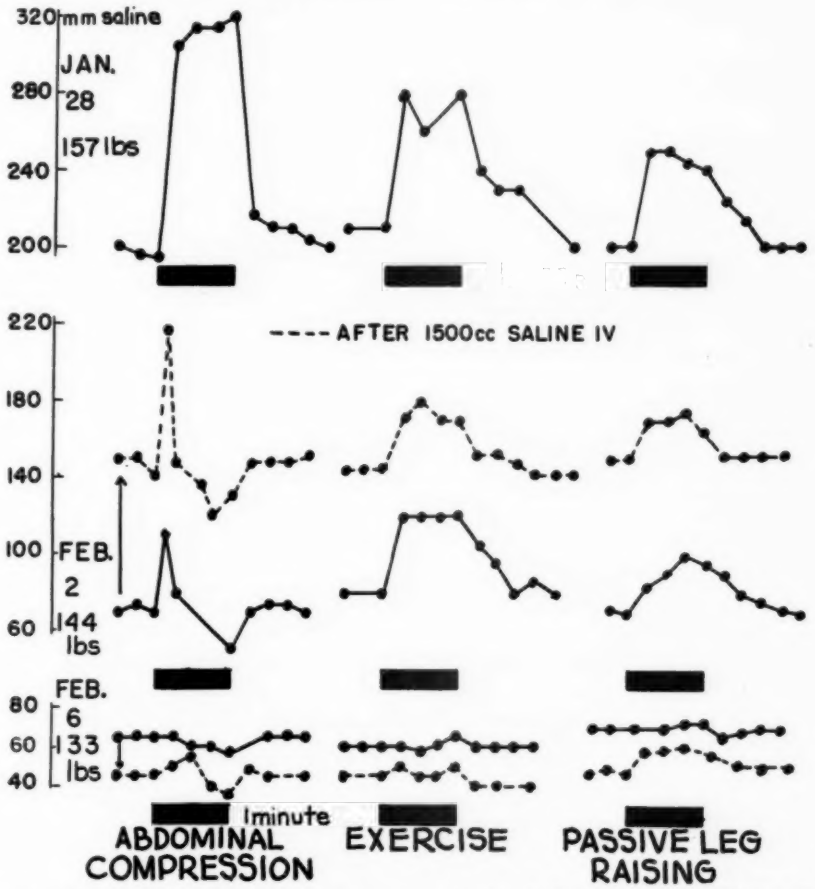
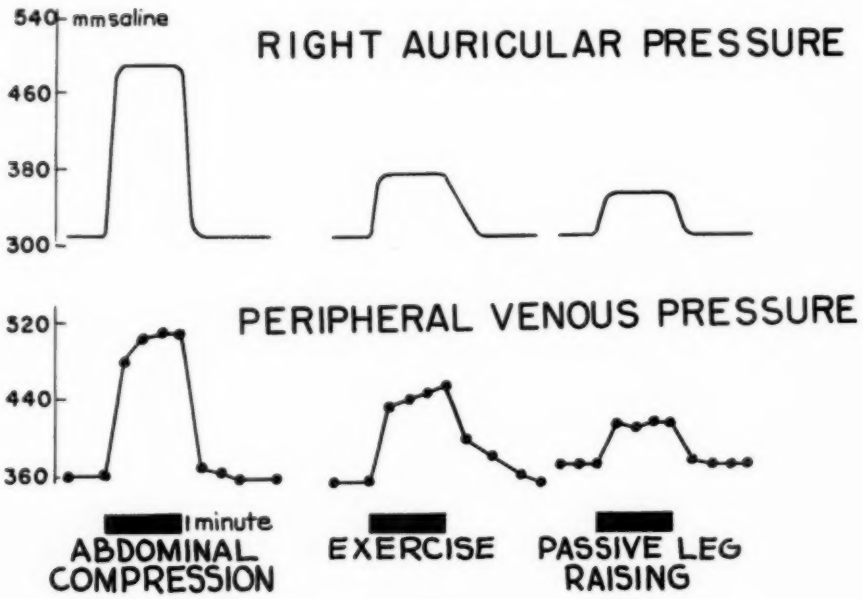
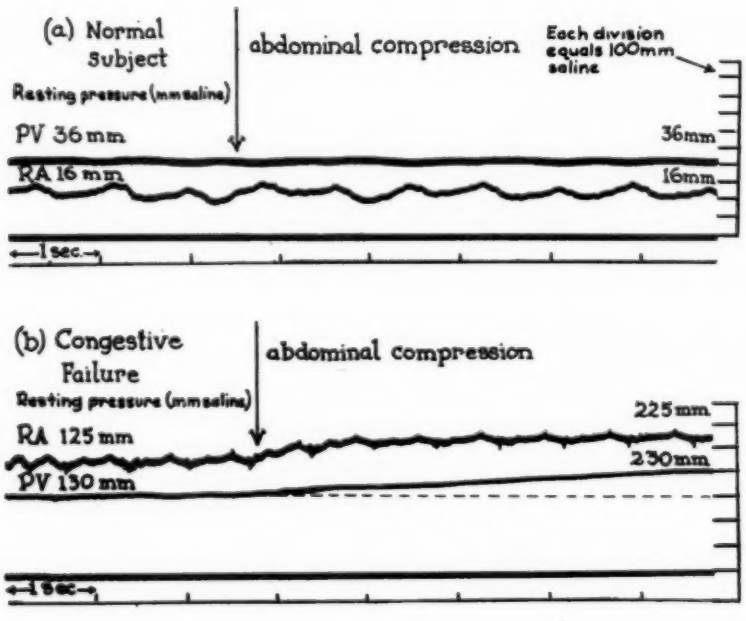


Fig. 2.—Alterations in venous pressure responses occurring during routine ward therapy for congestive failure and showing the effect of the administration of 1500 c.c. of saline intravenously. Case 15.

In five patients responses to the three maneuvers were normal. Five other patients exhibited abnormal responses to one or more of the procedures. In two of these patients abdominal compression responses occurred which were unlike those obtained in normal subjects. During abdominal compression there was a transient rise and then a fall to the control level. This type of re-



A.



B.

Fig. 3.—*A*, changes of auricular and peripheral venous pressure measured simultaneously during test maneuvers. Uppermost curve drawn from tracing made with Hamilton manometer. Peripheral venous pressure measured in arm by phlebomanometer. *B*, lower two tracings are reproductions of responses to abdominal compression in a normal subject and a patient with congestive failure. Responses were determined by a Hamilton manometer connected to a needle in the vein (PV) and to a venous catheter with the tip in the right auricle (RA).

sponse has been observed in patients recovering from congestive failure. A definite rise in pressure occurred during exercise. No significant change took place on leg raising. Of the remaining three subjects, one showed the diphasic type of response to abdominal compression. The other two had abnormal responses to exercise, although their response to abdominal compression was within normal limits. It is of interest that in one of these patients the intravenous infusion of 500 c.c. of normal saline solution produced an acute attack of dyspnea and coughing, although his venous pressure rose only 10 millimeters.

D. *Changes in right auricular pressure.*—In nine subjects measurements of right auricular pressure were made. The results were similar to those obtained with peripheral venous pressures. In one normal subject (Case 33) the right auricular pressure rose 30 mm. during exercise. This may have been due to changes of intrathoracic pressure dependent on fixation of the rib cage, which cannot always be eliminated. The response to abdominal compression was normal. In two subjects simultaneous recording of the right auricular and peripheral venous pressure indicated that the responses were identical quantitatively and qualitatively (Table II,A and II,B). No time difference was noted between the onset of pressure rise in the vein and auricle upon beginning the maneuver (Fig. 3).

TABLE II, A. CHANGES IN RIGHT AURICULAR PRESSURE PRODUCED BY ABDOMINAL COMPRESSION, EXERCISE, AND PASSIVE LEG RAISING IN NORMAL SUBJECTS AND PATIENTS WITH CLINICAL EVIDENCE OF RIGHT-SIDED HEART FAILURE

CASE NUMBER	AURICULAR PRESSURE (MM. OF SALINE)*				REMARKS†
	RESTING LEVEL	CHANGE WITH ABDOMINAL COMPRESSION	CHANGE WITH EXERCISE	CHANGE WITH LEG RAISING	
31	−38	+25	N.D.	N.D.	Normal subject
32	−60	0	0	0	Normal subject
33	16	−18	+30	0	Normal subject
34	27	− 9	N.D.	N.D.	Normal subject
16	367	+115	+61	+62	ASHD
15	131	+105	+87	+61	ASHD
20	118	+108	+54	+54	CP
18	77	+222	+88	+34	CP
35	111	+122	+20	N.D.	RHD, MS

*N.D., not determined.

†ASHD, arteriosclerotic heart disease; CP, constrictive pericarditis; RHD, rheumatic heart disease; MS, mitral stenosis.

TABLE II, B. SIMULTANEOUS RESPONSE OF PRESSURE IN PERIPHERAL VEIN AND RIGHT AURICLE TO ABDOMINAL COMPRESSION, EXERCISE AND PASSIVE LEG RAISING

LOCATION	RESTING LEVEL	CHANGE WITH ABDOMINAL COMPRESSION	CHANGE WITH EXERCISE	CHANGE WITH LEG RAISING	REMARKS*
Right auricle	309	+169	+67	+47	Case 20
Peripheral vein	360	+160	+100	+30	CP

*CP, constrictive pericarditis.

E. *Effect of intravenous infusions upon the venous pressure responses.*—The response of venous pressure to the intravenous infusion of fluid has been advocated[2] as a test of cardiac competence. It is reported that a normal subject will show only a slight elevation of pressure while a subject with heart failure will show a greater rise. The response will depend upon the rate at which the injection is given as well as upon whether it be saline or albumin. In the present study, intravenous infusions of isotonic saline solutions and albumin into two normal subjects produced elevations in resting venous pressures, but did not change the normal venous pressure response to exercise, abdominal compression, and leg raising. In patients with congestive failure and abnormal responses to the maneuvers, elevation in venous pressure occurred after infusions, but the magnitude of the responses to the test procedure was not significantly altered except in one patient (Case 37), in whom a biphasic response to abdominal compression was altered so that a distinct, sustained elevation occurred when the maneuver was repeated after the infusion. This patient had severe hypertension, but the only evidence of heart failure was mild dyspnea on moderate exertion. A striking alteration in the response to infusions and the test maneuvers by routine therapy for congestive failure is demonstrated by Case 15 (Table III and Fig. 2).

TABLE III. THE EFFECT OF INTRAVENOUS INFUSIONS UPON THE VENOUS PRESSURE RESPONSES TO ABDOMINAL COMPRESSION, EXERCISE, AND PASSIVE LEG RAISING

CASE NUMBER	VENOUS PRESSURE (MM. OF SALINE)				HEART RATE	HEMATOCRIT	REMARKS*
	RESTING LEVEL	CHANGE WITH ABDOMINAL COMPRESSION	CHANGE WITH EXERCISE	CHANGE WITH LEG RAISING			
35	80	0	+10	+10	80	42	Normal subject
	150	−20	+10	+10	96	35	1500 c.c. saline, 50 Gm. albumin, 30 min.
36	90	0	0	+10	80	42	Normal subject
	120	+10	+20	0	90	36	1000 c.c. saline, 40 Gm. albumin, 1 hour
15	35	+40 −20	+40	+20	68		ASHD
	135	+50 −20	+40	+20	96		1000 c.c. saline, 1 hour
	30	+20	0	0	68		
	30	+20	0	0	80		1000 c.c. saline, 1 hour
17	90	+40	+40	+10	84		ASHD
	130	+60	+50	+10	90		1500 c.c. saline, 1 hour
13	90	+40	+45	+10	62	37	ASHD
	140	+70	+50	+20	64	32	1500 c.c. saline, 50 Gm. albumin, 30 minutes
10	166	+70	+30	+20	70	39	RHD, MS
	216	+120	+35	+30	75	36	1500 c.c. saline, 1 hour
37	40	−30 +20	+60	+40	70		ASHD
	110	+70	+70	+40	72		1500 c.c. saline, 30 minutes

*Saline, isotonic saline solution; albumin, human albumin solution; time notations, duration of the infusion; ASHD, arteriosclerotic heart disease; RHD, rheumatic heart disease; MS, mitral stenosis.

DISCUSSION

Three methods of increasing venous return to the right side of the heart have shown a consistent pattern of venous pressure responses both in subjects with a competent circulation and in patients with congestive failure. Of the three, the method of abdominal compression usually produced the greatest elevation of venous pressure, when an abnormal response occurred.

The changes in peripheral venous pressure were found to correspond closely to right auricular pressure and can, therefore, be considered for all practical purposes as a measure of the filling pressure of the right side of the heart.

Abnormal responses occurred consistently only in patients with clinical failure of the right side of the heart, who usually had elevated resting venous pressures. Patients with marked dyspnea and pulmonary congestion, but without peripheral congestion, have normal resting venous pressures and may give normal responses to the various test procedures, or the responses may be slightly abnormal, especially as regards the exercise test. It is quite possible that patients with early or latent right-sided heart failure, not evident by clinical signs or symptoms or by an elevation in the resting venous pressure, may be revealed by abnormal responses to the test maneuvers. This may be inferred from the fact that in several subjects the resting venous pressure was within normal limits although the response to the test maneuvers was abnormal. It was observed that as failure progressed the resting venous pressure became abnormally elevated and the responses became greater. The reverse occurred during therapy. Three patients with chronic constrictive pericarditis, without evidence of pulmonary congestion, gave abnormal responses; and in two of these the resting venous pressures were questionably elevated if at all. In these patients the embarrassment to right auricular filling was obvious.

Three possible physiological conditions may exist in the venous circuit which could give rise, singly or in combination, to the abnormal responses observed. These are an increase in peripheral venous tone produced by the maneuvers; a well-filled or distended venous system; and an inability of the right side of the heart to adjust itself quickly to a sudden increment of blood reaching it.

Although there are no studies bearing on the first of these three points the prompt rise and fall of the venous pressure when changes occur suggests that this is not an important factor. The latter two conditions may well operate in conjunction. When the venous system is not distended and when an increase in venous outflow is quickly absorbed by a right ventricle which is capable of readily increasing its output, no increase in pressure occurs when blood is displaced toward the heart and upper extremities from the portal system or the lower extremities by manual pressure or elevation of the legs, or when more blood reaches the veins from the arterial side of the circulation as in exercise. This is the response by a competent circulation. When, however, the venous reservoir is already distended and the outflow is impaired by a right ventricle which cannot promptly increase its output, then an increase in the blood volume occupying the venous system produces a rise in pressure. This occurs in heart failure with peripheral

congestion. The fact that there is not a progressive increase in the venous pressure as the various maneuvers continue suggests that an adjustment takes place at this level of pressure. This adjustment may be a somewhat delayed increase in right ventricular output resulting from the stimulus of the increase in venous, right auricular, and right ventricular diastolic pressure.

Some estimate of the relative importance of distention of the venous reservoir versus the competence of the right ventricle as factors responsible for the increase in venous pressure during the procedures described, may be gained from the effect of intravenous infusions. Such infusions temporarily increase the circulating blood volume and hence lead to greater filling of the venous channels, and often raise the venous pressure. If the further increase in pressure occasioned by the added blood displaced cephalad by the maneuvers is due mainly to the factor of a distended venous system, this pressure should be proportionally greater under such conditions of distention than when the veins were less congested before the infusion. If, however, the increment in pressure occurring with the maneuver is determined mainly by the ability of the right ventricle to accommodate itself to an increase in filling, the pressure change would be the same as before the infusion, since the amount of blood displaced remains the same. The latter was found to be true in subjects with both competent and incompetent circulations.

The fall in venous pressure which frequently occurs in normal subjects upon abdominal compression is probably due mainly to the shutting off of venous return from the caudal regions of the body through the inferior vena cava. That this results in a rise in venous pressure below the point of compression has been shown by the Bradleys,[12] who produced rises in pressure in the renal veins by abdominal tourniquets, and by the observed rise in venous pressure in the veins of the leg during abdominal compression in normal subjects studied in this laboratory. Borderline responses where the venous pressure first rises and then falls below normal have been demonstrated in cardiac patients during recovery from decompensation. Here both sets of conditions probably come into action.

This study demonstrates the practical value of these maneuvers in the clinical determination of the presence of right-sided heart failure, and gives evidence that valuable information may be obtained which a simple estimate of the resting venous pressure may not reveal. Of the three maneuvers, abdominal compression, the simplest to execute, is usually the most helpful. The application of these maneuvers also tends to minimize the importance of a standard reference point for the resting venous pressure, since it is the extent of the increase in pressure above the resting level which is measured and not the absolute level itself.

SUMMARY AND CONCLUSIONS

A study is reported of the response of the peripheral venous pressure to light exercise, to abdominal compression, and to passive elevation of the legs in normal subjects and in patients with various types and degrees of congestive heart failure. It has been shown that patients with clinical failure of the right side of the heart respond to these maneuvers with a significant increase in venous

pressure, whereas normal persons and patients with failure of the left side of the heart, without peripheral congestion, show no significant increase. Changes in right auricular pressure were found to correspond closely to the alterations in peripheral venous pressure. The rapid intravenous infusion of isotonic saline solution or albumin solution was found to elevate the resting venous pressure in subjects with both normal and incompetent circulations. The type and magnitude of the responses to the maneuvers were, however, not significantly altered during the infusions.

The physiological significance of the findings is discussed; and the practical value of these maneuvers in the estimate of failure of the right side of the heart is pointed out.

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Clinical Reports

DEVELOPMENT OF VENTRICULAR TACHYCARDIA FOLLOWING CAROTID SINUS STIMULATION IN PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA

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PAROXYSMAL supraventricular tachycardia is sometimes stopped by carotid sinus stimulation.[1-10] When this procedure is effective, the tachycardia is generally followed by reversion to sinus rhythm. Sometimes, it is preceded by nodal escape. The two patients here reported responded in an unusual manner to carotid pressure. Instead of sinus rhythm, they developed a ventricular tachycardia which was later replaced by sinus rhythm. Neither patient showed any other evidence of heart disease.

CASE REPORTS

Case 1.—A 35-year-old white woman had had attacks of tachycardia over a period of several years. These attacks were manifested by sudden onset of symptoms of rapid palpitations, apprehension, and sweating. The duration of these episodes varied from a few minutes to several hours before ceasing abruptly. The attack which brought her to the hospital on Feb. 7, 1942 occurred about one-half hour before arrival. There was no other history suggesting heart disease.

On arrival at the hospital she was extremely apprehensive, was perspiring profusely, and her pulse was found to be 200. The remainder of the physical examination was normal.

An electrocardiogram was immediately obtained and showed a supraventricular tachycardia with a rate of 204. Carotid sinus pressure was applied and immediately ventricular tachycardia developed (Fig. 1). After a brief run of this arrhythmia shorter runs occurred interspersed by a few normal beats before reversion to normal sinus rhythm. With the cessation of the tachycardia the patient's symptoms subsided at once. Subsequent electrocardiograms were normal.

She has been followed for seven years since this episode and has been asymptomatic except for a very occasional recurrence of tachycardia. No evidence of heart disease has developed.

Case 2.—A 43-year-old white woman had had attacks of rapid heart rate over a period of ten to twelve years. These were characterized by sudden onset and abrupt cessation, lasting from a few seconds to as long as six hours, and were accompanied by weakness, apprehension, sweating, and pallor. They seemed to occur more often when she was "nervous" and in the premenstrual period.

One year before she was diagnosed as having chronic myelogenous leucemia and received x-ray therapy intermittantly afterward.

About one week prior to admission to the hospital she developed chills, fevers, malaise, nausea, vomiting, and mild diarrhea. These symptoms persisted and she was admitted to this hospital for diagnosis and treatment on Aug. 18, 1949.

She was found to be well developed and well nourished, but appeared acutely ill. Her fever was 103° F., her pulse 88, and blood pressure 164/90. Her skin was warm and moist and her pulse felt normal. Abdominal examination revealed slight generalized tenderness and the liver and spleen could be felt nine and seven centimeters, respectively, below the costal margins.

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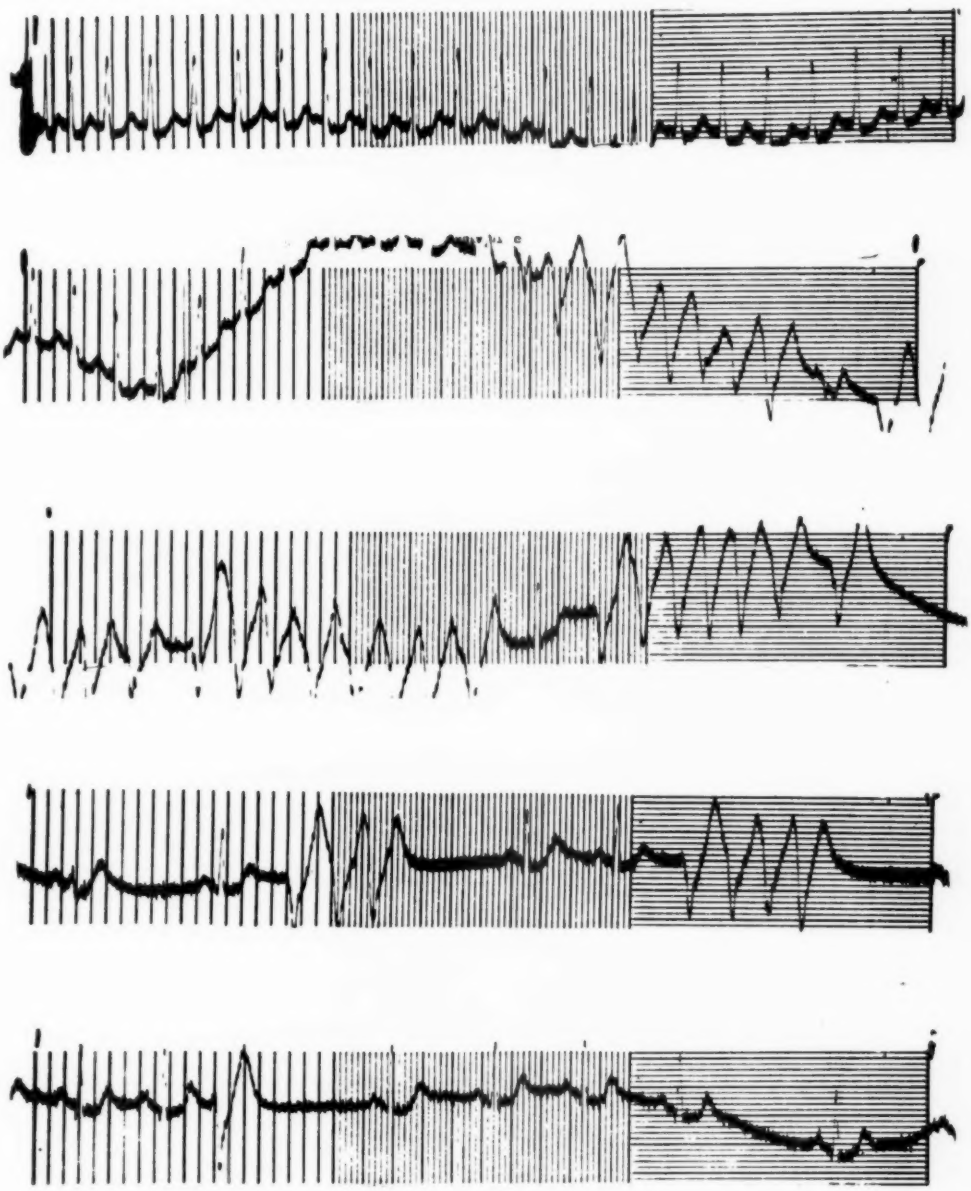

Fig. 1.—Electrocardiogram (Lead II) showing the development of ventricular tachycardia following carotid sinus stimulation in Case 1.

Her red blood count was 3.58 million with 70 per cent hemoglobin, and her white blood count was 24,700 with 69 per cent polymorphonuclear leucocytes, 25 per cent lymphocytes, 4 per cent monocytes, and 1 per cent eosinophils and basophils. A urine analysis showed four plus albuminuria and 18 to 20 white cells. Cultures of the blood, urine, and feces were negative for pathogenic organisms. Agglutinations for typhoid "O" and "H" antigens were strongly positive.

The patient was started on 300,000 units of penicillin daily on the day following admission. However, her condition remained unchanged.

On the fifth hospital day the patient suddenly developed a tachycardia of 200 with apprehension, sweating, weakness, and pallor. An electrocardiogram revealed a supraventricular tachycardia with a rate of 200. Carotid sinus pressure was first applied on the right without effect. However, when applied on the left a ventricular tachycardia developed immediately which reverted to sinus rhythm after a short run (Fig. 2). With the establishment of the sinus rhythm, the patient was relieved of her symptoms. The following day two more episodes occurred, one of which stopped spontaneously and the other required digitalization and carotid sinus pressure. Unfortunately no tracings were obtained. There have been no other recurrences thus far.

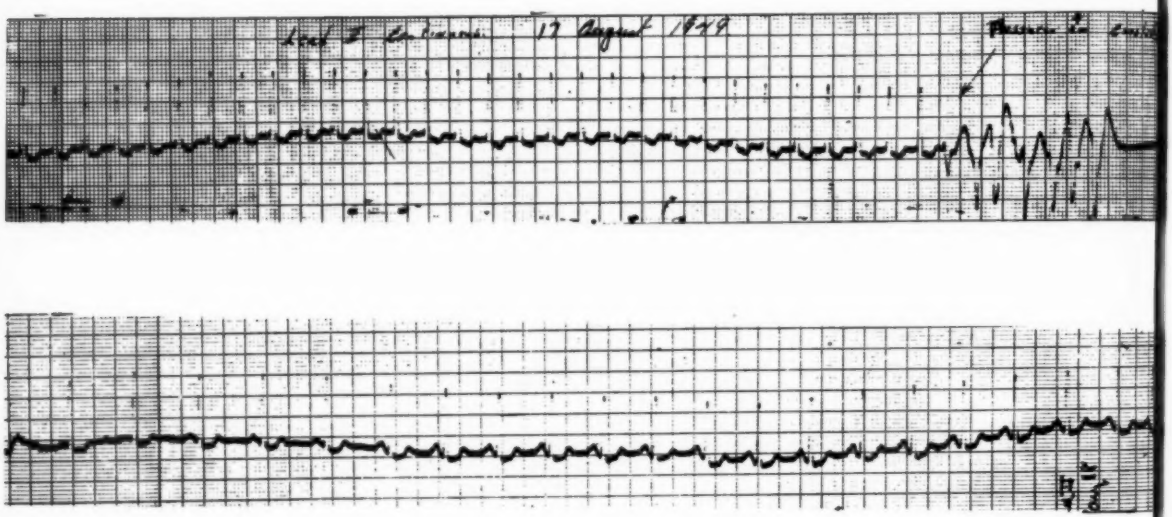

Fig. 2.—Electrocardiogram (Lead II) showing supraventricular tachycardia and the development of ventricular tachycardia after carotid sinus pressure in Case 2.

SUMMARY

Two reports of paroxysmal supraventricular tachycardia have been presented in which the patients developed ventricular tachycardia following carotid sinus stimulation before reverting to normal sinus rhythm.

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A CASE OF CONGENITAL HEART DISEASE

Truncus Aorticus Solitarius, Single Ventricle, and Aberrant Coronary Drainage Into the Common Ventricle

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THIS case is reported to present a rare complex cardiac anomaly, one feature of which (the aberrant coronary venous drainage) is, as far as can be determined, unique to the medical literature. It also serves to re-emphasize particular clinical criteria in the diagnosis of truncus aorticus solitarius and single ventricle, and illustrates the accuracy of diagnosis possible with cardiac catheterization and angiocardiography.

CASE REPORT

A 5½-year-old girl was referred to the Michael Reese Hospital by one of us (S. G.) for special studies. The parents were first told that the child had "heart trouble" when she was 1 year of age. The child had always been pale, and the parents stated that her lips always had a slight bluish cast. Dyspnea on slight exertion was noted since the age of about 1 year. There was no history of ankle edema, orthopnea or precordial pain. Treatment until the present hospital admission consisted solely of limitation of activity. The patient's neonatal period was apparently normal. She had chicken pox at the age of 2½ years. Inquiry revealed no unusual susceptibility to upper respiratory infections. There was no familial history of congenital heart disease.

Physical examination revealed a responsive, well-developed, well-nourished, white girl. There was slight cyanosis of the lips and nail-beds. Exercise caused an increase in cyanosis. No clubbing was noted. The left side of the chest was more convex than the right. The lungs were clear to percussion and ausculation. The apex impulse was felt best in the fourth and fifth intercostal spaces just to the left of the mid-clavicular line. All the heart sounds were loud, with the mitral second sound being very forceful. The second sound was heard more loudly to the left of the sternum in the second intercostal space than on the right. No murmurs were heard. The pulse rate varied from 72 to 130 beats per minute. Blood pressure was 86/68 mm. of mercury. The radial and femoral pulses were of good quality and equal bilaterally.

Laboratory studies were as follows: hemoglobin, 17.2 grams (110 per cent); red blood cells, 5.54 millions; white blood cells, 10,000; sedimentation rate (Wintrobe) 2 mm. per hour. Urinalysis was normal.

Special Studies.—

Fluoroscopy: The shadow comprising the base of the heart was extremely wide in the postero-anterior view. The aorta was distinguishable within this shadow as a large vessel, and the right border of the shadow was formed by the superior vena cava. The aortic knob was visible in this

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position. The cardiac apex was lifted off of the diaphragm. The left hilus was seen as a rounded fairly well-defined area of increased density; the right hilus was not visible. There was no hilar dance. The oblique positions revealed no abnormalities. The lungs were clear and the diaphragmatic movements normal. X-ray films confirmed the presence of a large aorta (Fig. 1).

Electrocardiography: The complete electrocardiogram is shown in Fig. 2. The tracings are compatible with the presence of a right heart strain pattern.

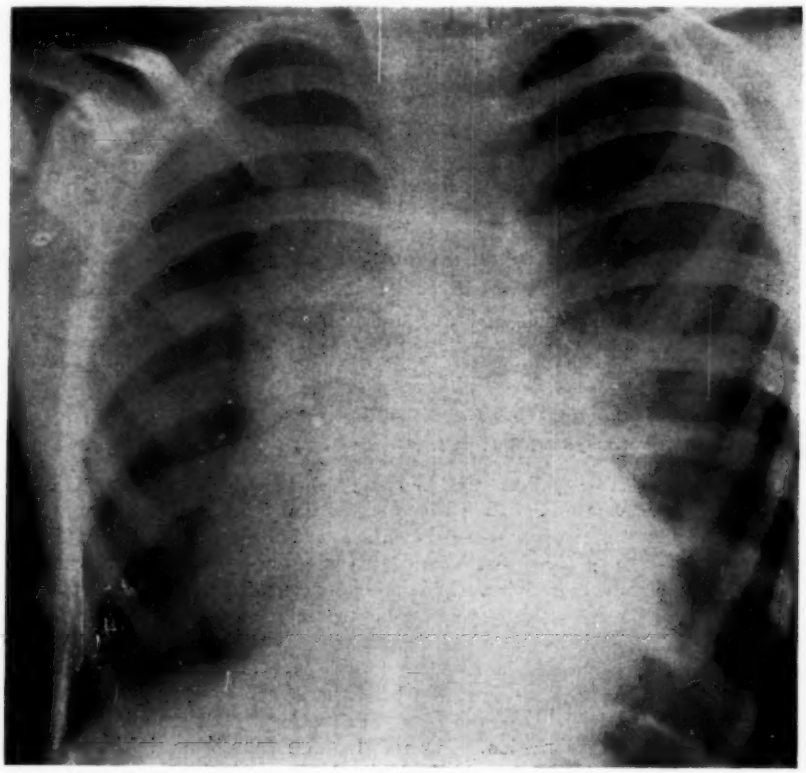

Fig. 1.—X-ray taken in the posteroanterior position. The left hilus is seen as a rounded area of density. Note the width of the shadow comprising the base of the heart. The aorta is clearly seen within this shadow.

Cardiac Catheterization: This procedure was done under sodium pentobarbital sedation.* The catheter was introduced into the left median basilic vein and advanced through the right atrium into the ventricle. Under fluoroscopic control, the tip of the catheter was readily moved all the way to the left cardiac border. The catheter tip was then placed in the usual site for entering the pulmonary artery, but repeated attempts to enter this vessel were unsuccessful. During one of the manipulations, the catheter tip took a peculiar turn to proceed along the left border of the heart shadow toward the apex (Fig. 3). It was suspected that the catheter tip had passed outside the ventricular cavity. Pressure tracings substantiated this impression, the contour of the tracings being unlike those expected from the pulmonary artery or ventricular cavity (Fig. 4). Two blood samples were drawn from slightly different positions in this aberrant vessel, their oxygen contents determined later being only 5.7 and 6.5 volumes per cent. A continuous pressure tracing was then obtained as the catheter was withdrawn under fluoroscopic control.

*We are indebted to Dr. B. Stodsky of the Anesthesia Department, Michael Reese Hospital, for his supervision of the anesthesia.

Both fluoroscopy and the pressure tracing confirmed that this aberrant channel opened directly into the ventricular cavity which was later proved to be a common ventricle.

Interpretation of cardiac catheterization results: The data on oxygen determinations and pressures are summarized in Table I. The marked difference in oxygen contents between auricular and ventricular blood indicates a left-to-right shunt in the ventricle. The oxygen content of the arterial blood being only 16.9 volumes per cent as compared to the oxygen capacity of 20.7 volumes per cent is indicative of a right-to-left shunt. Furthermore, the close similarity between the oxygen content of arterial blood (16.9 volumes per cent) and the oxygen contents of the samples from the ventricle (15.3, 16.4, and 16.6 volumes per cent) points to nearly complete mixing inside the ventricular cavity, and in view of the other findings, indicates the diagnosis of a functional single ventricle.

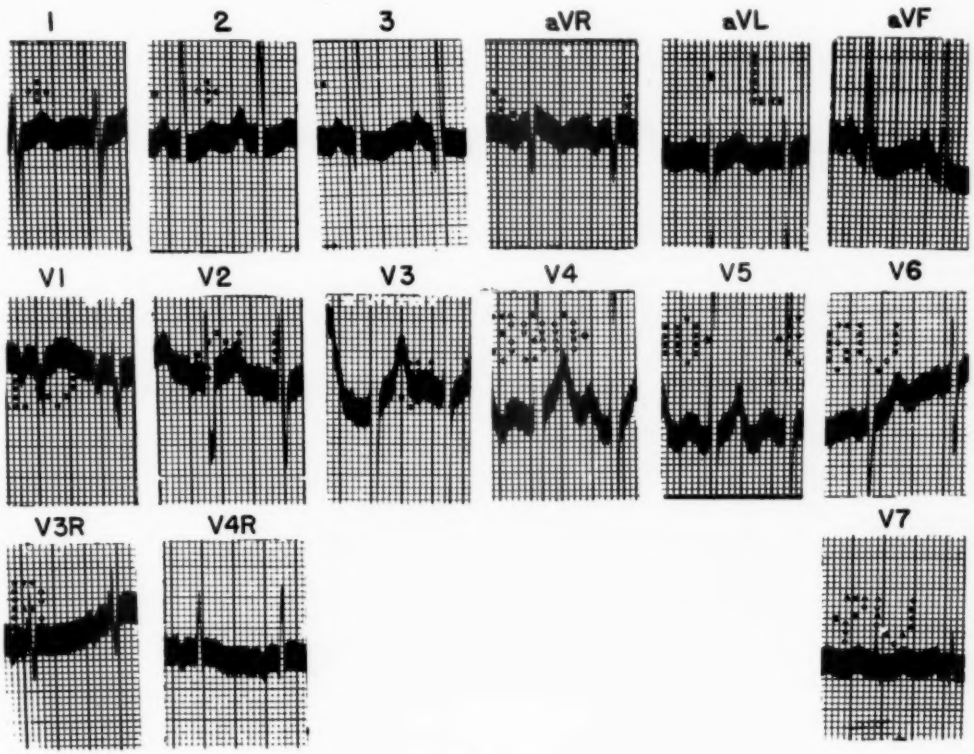

Fig. 2.—Electrocardiogram. Discussed in text.

It is believed that the presence of an aberrant vessel entering the common ventricle is proved by the fluoroscopic observations and the continuous pressure tracings showing a rapid transition from an unusual pressure contour to that typical of the ventricular cavity. The extremely low oxygen contents of blood samples drawn from this vessel indicate it to be draining myocardial venous blood.

The pressures obtained from the single ventricle are as expected, inasmuch as this chamber is the pump for blood to both the pulmonary and systemic circuits.

Two problems remained unsolved after cardiac catheterization: (a) What is the status of the pulmonary arteries? (b) Is an inter-auricular septal defect present? Accordingly, angiocardiography was performed.

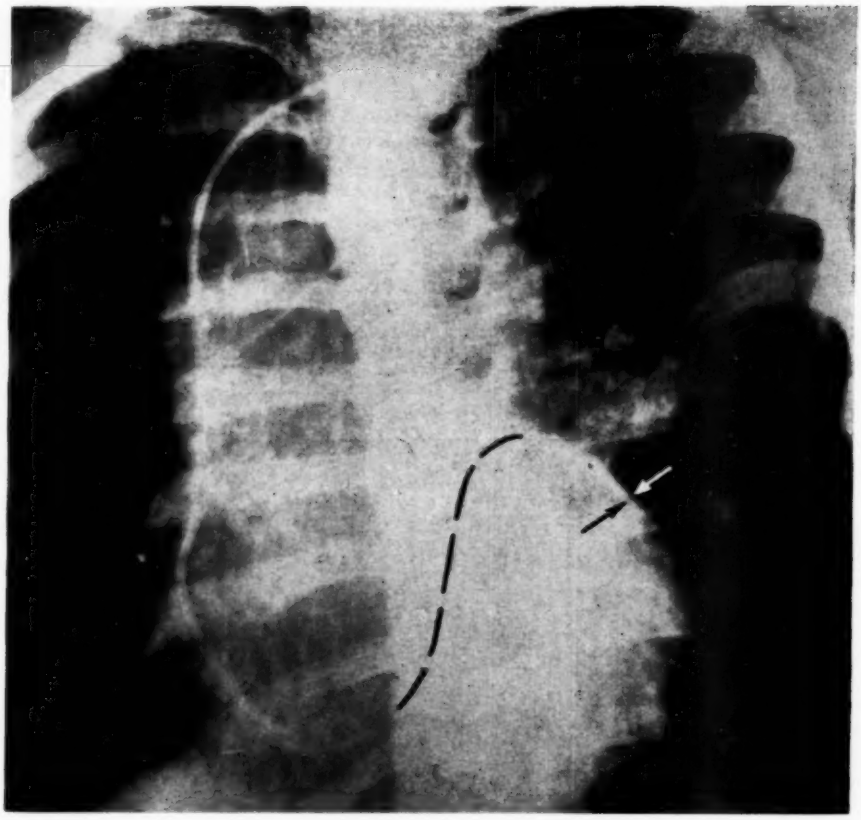

Fig. 3.—X-ray (anteroposterior position) of catheter within aberrant venous channel draining into single ventricle. Arrows delineate the tip of the catheter.

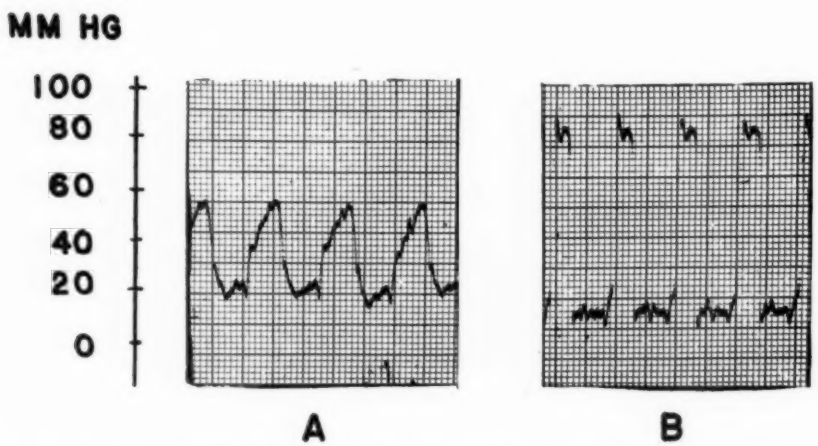

Fig. 4.—(A) Pressure tracing from aberrant vessel draining into single ventricle. (B) Pressure tracing from single ventricle.

Angiocardiography: 35 c.c. of 70 per cent Diodrast solution* was rapidly injected, with the child sitting erect in the left anterior oblique position.

Figure 5 illustrates the key findings. The aorta and "pulmonary" artery were visualized simultaneously. The "pulmonary" artery is seen to end bluntly at the end proximal to the heart. It overlies the descending aorta in part, and there is no apparent connection to either the base of the heart or to the ascending aorta. It is concluded, therefore, that this vessel filled from the descending aorta, either directly or via a patent ductus arteriosus. A coronary artery, arising from the base of the aorta, is visualized. There is dye in that part of the ventricle where, normally, the left ventricle is seen in the left anterior oblique position. No evidence for an interauricular septal defect was found.

TABLE I. CARDIAC CATHETERIZATION DATA

LOCATION OF CATHETER	OXYGEN CONTENT (VOLUMES PER CENT)	PRESSURE (MM. OF HG)
1. Right Atrium	13.10 12.15	5-0
2. Common Ventricle	16.64 16.37 15.27	92/10*
3. Aberrant Coronary Venous Channel	5.73 6.50	55/15
4. Femoral Artery	16.90	86/68 (cuff method)

*End-diastolic pressure.
Oxygen consumption (estimated): 150 c.c. per minute. Oxygen capacity of arterial blood: 20.69 volumes per cent. Systemic flow: 3.4 liters per minute. Flow through the lungs: 3.4 liters per minute.

Interpretation of Angiocardiography Results: Angiocardiographic studies confirmed the presence of a functional single ventricle. They established the fact that only one vessel arose from the base of the heart, and that this vessel was undoubtedly the aorta. Additional evidence for this was the visualization of a coronary artery. The anatomical peculiarities of the pulmonary blood supply were clarified, the presence of a pulmonary vascular supply via the aorta to the left lung being established.

DISCUSSION

The diagnosis of truncus aorticus solitarius is made, rather than that of truncus arteriosus communis persistens, because of the angiocardiographic evidence that the blood vessel supplying the lung originates from the descending aorta. There has been confusion in the literature because too frequently patients with solitary aortic or pulmonic trunks have been classified as having persistent truncus arteriosus. The latter term should be reserved for those instances in which there is evidence that separation between the aorta and pulmonary artery was never fully completed during embryological development. In other words, the defect originates because of a failure of the aortico-pulmonary septum to close. In such instances the pulmonary arteries originate from the common trunk near the base of the heart. In truncus aorticus solitarius the aorta is the sole

*Diodrast solution was kindly supplied by Winthrop-Stearns, Inc.

vessel arising from the base of the heart, and the structures which develop from the sixth branchial arch show varying degrees of regression or are completely absent. When complete atresia of structures arising from the sixth arch occurs, the only circulation to the lungs is via the bronchial arteries. Partial regression of structures from the sixth arch is more common than complete absence, the pulmonary trunk being present only as a fibrotic band, with blood flow into the pulmonary arteries (which also may show varying degrees of hypoplasia) through a patent ductus arteriosus.

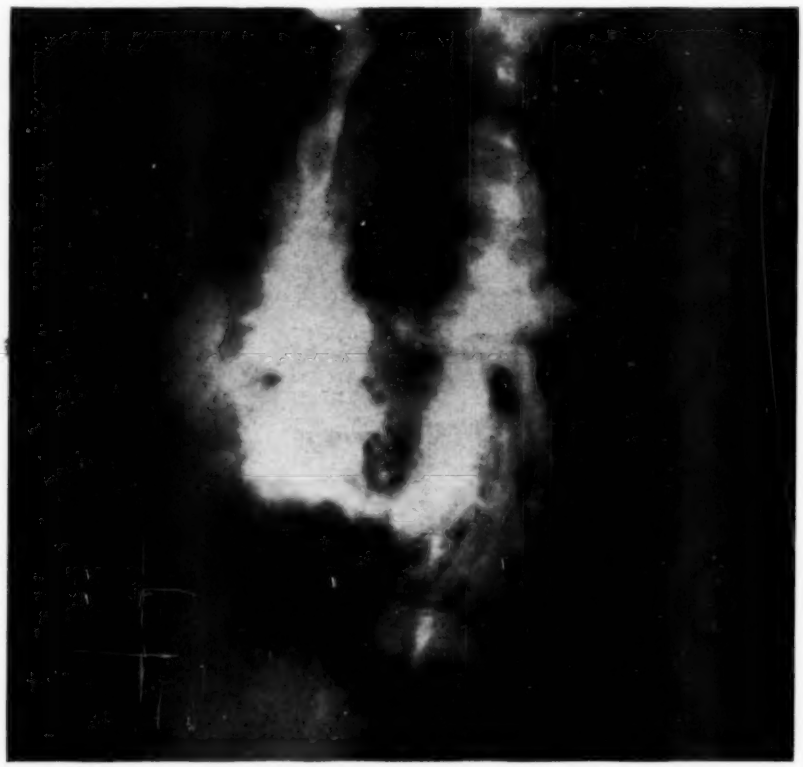

Fig. 5.—Angiocardiogram in left anterior oblique position. Note (a) a coronary artery arising from the base of the aorta, and (b) blunt ending of the "pulmonary" artery at the base of the heart.

Figure 5 clearly delimits the portion of the aorta with which the "pulmonary" artery must communicate. The point is beyond the aortic arch, and beyond that portion of the aorta from which we would expect a ductus arteriosus to come. Taussig[1] has cited a case of P. D. White's in which the circulation to the left lung was via a large branch from the descending aorta.

Humphreys,[2] in her excellent article on truncus communis persistens stated, with regard to truncus aorticus solitarius, that "the defect is a combination of varying degrees of transposition with atresia of the pulmonic element." However, the occurrence of transposition with solitary aortic trunk, though common, is not a consistent finding. Kugel[3] has cited two cases, in only one of which there

was transposition. Lev and Saphir[4] cite a case reported by Diaz and de los Reyes which they believe was most likely a truncus aorticus solitarius. The aorta also arose from the left ventricle in this instance. In the presence of a more complete septum than in our patient, the degree of transposition of the solitary trunk might be of considerable theoretical and practical interest.

The discovery of an anomalous coronary venous channel entering the common ventricle was, of course, a purely fortuitous circumstance. The pressure gradient between this aberrant vessel and the ventricle is such as to allow flow into the ventricle only during diastole. There is no evidence for coronary insufficiency, and, in all probability, this anomalous coronary venous drainage causes little or no impairment of coronary flow to the myocardium. Gregg and Shipley,[5] working on dogs, have shown that acute or chronic occlusion of the coronary sinus caused little interference with the functioning of the heart. These authors have stressed the role of the anterior cardiac veins and, together with Katz and his associates,[6] the many venous collateral channels in maintaining coronary venous flow.

Calculations, based on the assumption that the blood in the pulmonary veins is 95 per cent saturated, show that systemic and pulmonary flows are equal (3.4 liters per minute). Therefore, the cardiac output in this heart, with a functional single ventricle and a single outlet vessel, is about 7.0 liters per minute. The lungs are perfused through the same pressure head as the systemic circuit, and the potential energy of the heart is greater than that of the normal circulation. The calculated value for the potential energy of the heart in our patient is 1092×10^3 Gm. cm. per minute. The mean velocity of blood flow through the solitary aortic trunk, as calculated by the method developed in this laboratory,[7] is relatively small, being only 28 cm. per second. This is due to the tachycardia (150 beats per min.) and hence small stroke output (50 c.c.) and to the relatively large cross sectional area of the solitary trunk. The kinetic energy amounts, therefore, to 20 Gm. cm. per beat, and 3000 Gm. cm. per minute.

The absence of marked cyanosis in the presence of a functional single ventricle is of considerable interest, and can be explained only on the basis of a relatively adequate pulmonary flow. There are two possible situations which may directly affect the pulmonary circulation. One such situation is a sudden decrease of the peripheral resistance in the systemic circuit. It may be logically postulated, because of the anatomic abnormalities in this patient, that with the shift of more blood to the periphery, the pulmonary blood flow will decrease. We believe that, to a certain degree, this change does occur with exercise, and that it is the cause of the increased cyanosis.

The other possible situation affecting pulmonary blood flow involves an increased resistance in the lungs. The effect of pulmonary hypertension, such as is seen in the presence of a patent ductus arteriosus, on the development of structural changes in the arteriolar walls is still a subject of controversy. Should such a relationship be accepted, the high pressure head operating across the lung circuit in this patient would tend to cause progressive sclerotic changes in the arteriolar bed. The increasing peripheral resistance associated with such changes would tend to diminish pulmonary flow.

Certain diagnostic criteria may be re-emphasized on the basis of the findings in this patient. In a child, a large aorta, with the aortic knob clearly visible in the posteroanterior view on fluoroscopy, suggests the possibility of a truncus of some sort. A normal-sized heart, with no murmurs and only a mild cyanosis suggests the possibility of a single ventricle.

SUMMARY

A case of congenital heart disease is presented in which a truncus aorticus solitarius was diagnosed because the only vessel leaving the base of the heart was identified as the aorta by angiocardiography. The presence of a functional single ventricle was diagnosed on the basis of the close agreement of oxygen contents in samples obtained from various points in the ventricle and from the peripheral artery. The existence of an aberrant vein draining the myocardium and opening into the common ventricle was indicated by (a) continuous pressure tracings, and (b) the low oxygen content of blood samples taken from this channel.

Angiocardiography demonstrated that the pulmonary circulation was via the truncus aorticus solitarius, the descending portion of which gave rise to a large artery supplying the left lung. It is assumed that the right lung received its circulation via small bronchial arteries.

The presence of only mild cyanosis at rest, the fluoroscopic contour of the heart and the absence of murmurs are important signs in the clinical diagnosis of a single ventricle. A large vessel from the base of the heart and a visible aortic knob in the posteroanterior position on fluoroscopy in a child indicates the possibility of a truncus.

In this patient, the calculated flow through the pulmonary circuit is equal to that through the systemic circuit. The cardiac output from the common ventricle equals that expected from two separate ventricles. However, the heart, working against a single high pressure circuit, has to develop a much higher potential energy than under normal anatomical circumstances. The kinetic energy of this heart is not much increased, mainly because of the large calibre of the single outlet channel.

This case is unique in that a review of the literature has failed to reveal any reports of aberrant myocardial venous drainage such as that described above.

We are indebted to the other members of the department at Michael Reese Hospital for their assistance.

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TRUNCUS ARTERIOSUS COMMUNIS PERSISTENS

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BUCHANAN[1] in 1864, made one of the earliest reports of a patient with truncus arteriosus communis persistens, and, in 1890, Preisz[2] described the condition accurately. Since then opinions have fluctuated regarding the exact pathogenesis and pathological anatomy of this cardiovascular anomaly. Originally the condition was considered to consist of a single efferent trunk with *four* valve cusps giving rise to both pulmonary and systemic arterial circulations. The four cusps were considered necessary because: (1) embryologically four distal bulbar swellings (anlage of the cusps) are present before the aorticopulmonary septum divides them; (2) the aorticopulmonary septum is formed by the fusion of paired spurs between the fourth and sixth pair of aortic arches, and its caudal extension divides the common efferent trunk into aortic and pulmonary arteries; (3) the septum divides the larger, lateral, distal bulbar swellings to produce three swellings for each artery as anlage for the semilunar cusps. However, patients with common truncus were reported who had only three cusps with a rudimentary fourth cusp,[1,3] only two cusps,[4] and only three cusps, but all were similar in other respects. Thus, failure of development of one or more cusps from the distal bulbar swellings apparently could occur, and four cusps for the arterial trunk were no longer regarded as necessary for the diagnosis of truncus arteriosus communis persistens.[5-7]

The requisite diagnostic features were best set forth by Humphreys'[7] analysis of the literature in which she included fifteen definite instances and five possible ones. The additional criteria, as stated by Humphreys, demanded that only one large arterial trunk, approximately the size of two, should leave the base of the heart. This single trunk should combine the features and functions of both the aorta and the pulmonary artery, thereby giving rise to the coronary and systemic circulation, as well as supplying blood to the lungs. The anomaly was catalogued as "complete" when the pulmonary arteries arose separately from the common trunk, or when the sixth arch structures failed to develop and the arterial blood reached the lungs through collateral channels (usually bronchial arteries). It was called a "partial" defect when an incomplete septum separated a short pulmonic trunk which gave off the pulmonary arteries and occasionally a ductus arteriosus. There must be an interventricular defect in the posterior portion of the anterior septum of Rokitansky. Varying degrees of detorsion of the truncus are present. The truncus may override the septal defect or, in extreme cases, arise above the right ventricle. The crista supraventricularis propria

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TABLE I. ANALYSIS OF PATIENTS WITH TRUNCUS ARTERIOSUS PERSISTENS

TYPE		NUMBER OF PATIENTS	SEX*		SURVIVAL			FOUR CUSPS	SINGLE VENTRICLE	DEGREE OF CYANOSIS			
			M	F	OVER TWO YEARS	OVER TEN YEARS	MAXIMUM			TERMINAL	MINIMAL	EXTREME	NOT STATED
Type I—Patients with common pulmonary trunk with a patent ductus arteriosus[2,7]		3	1	1	0	0	2½ mo.	2	0	0	0	0	3
Type II—Patients with common pulmonary trunk without a patent ductus arteriosus[3, 12-27]		16	9	4	2	2 (12.5%)	17 yr.	6	1	4	6	0	6
Type III—Patients with two separate pulmonary arteries[1,3-6,24-26]		15	5	6	3	3 (20.0%)	36 yr.	0	5	3	3	0	8
Type IV—Patients with one pulmonary artery and remaining lung supplied by collaterals author.[9, 10]		3	2	1	1	1	35 yr.	0	0	0	1	0	2
Type V—Patients with no remnants of the sixth arch[2,5,31,33,37-50]†		18	8	9	5	4 (22.2%)	33 yr.	2	1	0	9	1	8
TOTALS		55	25	21	11	10	36 yr.	10	7	7	20	1	27

*Sex not stated for all patients.
†Includes two patients with possible ductus arteriosus as blood supply to both lungs.

(Spitzer) should terminate at the base of the septum beneath the ostium of the truncus. Defects in the foramen ovale or auricular septum are varied according to the degree of detorsion at the venous end of the heart. The mitral and tricuspid leaflets show modification of form and attachment according to the degree of shift of the trunk to the right.

The persistent common truncus arteriosus can be confused with the truncus solitarius aorticus in which there has been a complete division between the aorta and pulmonary artery, but the pulmonary artery is narrowed and fails to grow normally. When the pulmonary artery is obliterated at its orifice, there may be complete atresia, with a remnant of the pulmonary artery or an atretic cord persisting.[5,8] When remnants of the sixth arch are found, differentiation is easy, but when they are absent it is difficult to separate cases involving aplasia of the sixth arch structures from those involving atresia of the pulmonary trunk after division by the aorticopulmonary septum. In both instances there is a single trunk without trace of a pulmonary artery, and pulmonic circulation is maintained through collateral vessels (usually bronchial arteries).

There are five distinct patterns which the pulmonary circulation might adopt in patients with truncus arteriosus persistens (Table I): (1) common pulmonic trunk with patent ductus arteriosus; (2) common pulmonic trunk without a patent ductus arteriosus; (3) separate origin of the pulmonary arteries; (4) a pulmonary artery to one lung, the other lung being supplied by collaterals; (5) no remnants of the sixth arch, with both lungs supplied by collaterals. Because these anomalies are unusual and the clinical material meager, and because survival beyond the third decade of life is rare, the following case report is presented. In a case reported by Carr, Goodale, and Rockwell[4] the patient lived a year longer than the one described in this report.

CASE REPORT

R. W., a 35-year-old white woman, born Aug. 23, 1912, was admitted to the Presbyterian Hospital in Philadelphia, on the medical service of Doctor J. Roderick Kitchell, on Jan. 29, 1948, with a chief complaint of weakness, dyspnea, and edema.

Medical History: The patient had been continuously cyanotic since birth, with moderate exertional dyspnea and increased cyanosis on exertion, never having been able to engage in competitive sports. Until her terminal illness, however, she participated in church activities, attended the theater, and kept house with her mother. She had had measles and chicken pox in childhood, influenza in 1929, and frequent colds throughout her life. Her first serious illness, scarlet fever, occurred in 1939, followed by "dropsy" which cleared under her physician's care. At that time the blood urea nitrogen was 42.8 mg. per 100 ml. of blood, but five months later it was 16 mg. per 100 milliliters.

From 1941 to 1944 she had been under the observation of Dr. G. C. Griffith, cardiologist to the Presbyterian Hospital. Her complaints were chiefly related to the gastrointestinal tract, but physical examination at that time showed moderate cyanosis of the lips, nose, and nail beds; clubbing of the fingers and toes; darkness and fullness of the retinal veins; Grade 3 cardiac enlargement; a to-and-fro murmur with a loud, harsh systolic phase over the precordium best heard in the third left intercostal space next to the sternum. There was an accompanying systolic thrill. The murmur was also evident over the pulmonic area and one could not be certain whether there were two different murmurs. The blood pressure was 122/80; the pulse 78 and regular. There were occasional râles at the lung bases. The liver edge was barely palpable. There was no ankle edema. From Jan. 27 to Jan. 30, 1942, the patient was studied briefly at the Graduate

Hospital of the University of Pennsylvania because of recurrent pain in the right lower quadrant of the abdomen. An x-ray examination of the chest was reported as showing considerable increase in prominence of the pulmonary conus, and calcification near the left border in the midposition of the heart (Fig. 1, *A* and *B*). The patient was discharged with a diagnosis of (1), congenital heart disease and (2) colitis. She improved markedly under antispasmodic, sedative and dietary treatment, and, except for periodic examinations, required little medical attention

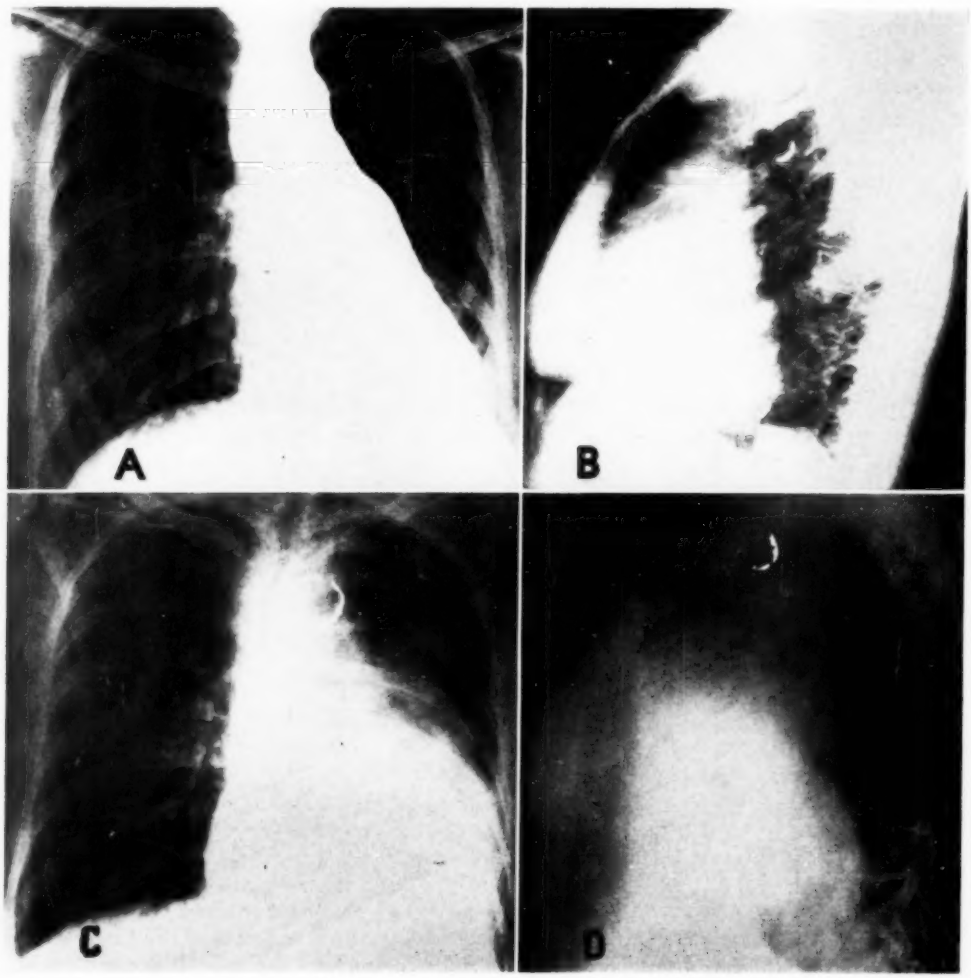

Fig. 1.—*A* and *B*, Posteroanterior and lateral roentgenograms of the chest taken in 1942 at Graduate Hospital. Note the prominence of the pulmonary conus, presence of a hilar "comma" shadow, relative dextroposition of the right border of the aorta, and marked enlargement of right and left ventricles. *C* and *D*, Anteroposterior and lateral views of the chest taken in 1948 at Presbyterian Hospital. There is accentuation of the previous findings. The calcification in the aortic arch and truncus valve is more evident.

She remained in fair health until five weeks prior to her admission to the hospital when she developed anorexia, nausea, and diarrhea accompanied by an upper respiratory tract infection. Two weeks later she developed dependent edema, which responded to digitalis and diuretic therapy. She was gradually allowed out of bed. However, recurring edema, dyspnea, and increased cyanosis required admission to the hospital.

Family History: There was no history of congenital heart disease elsewhere in the family.

Social History: The patient went through high school and was not considered deficient mentally.

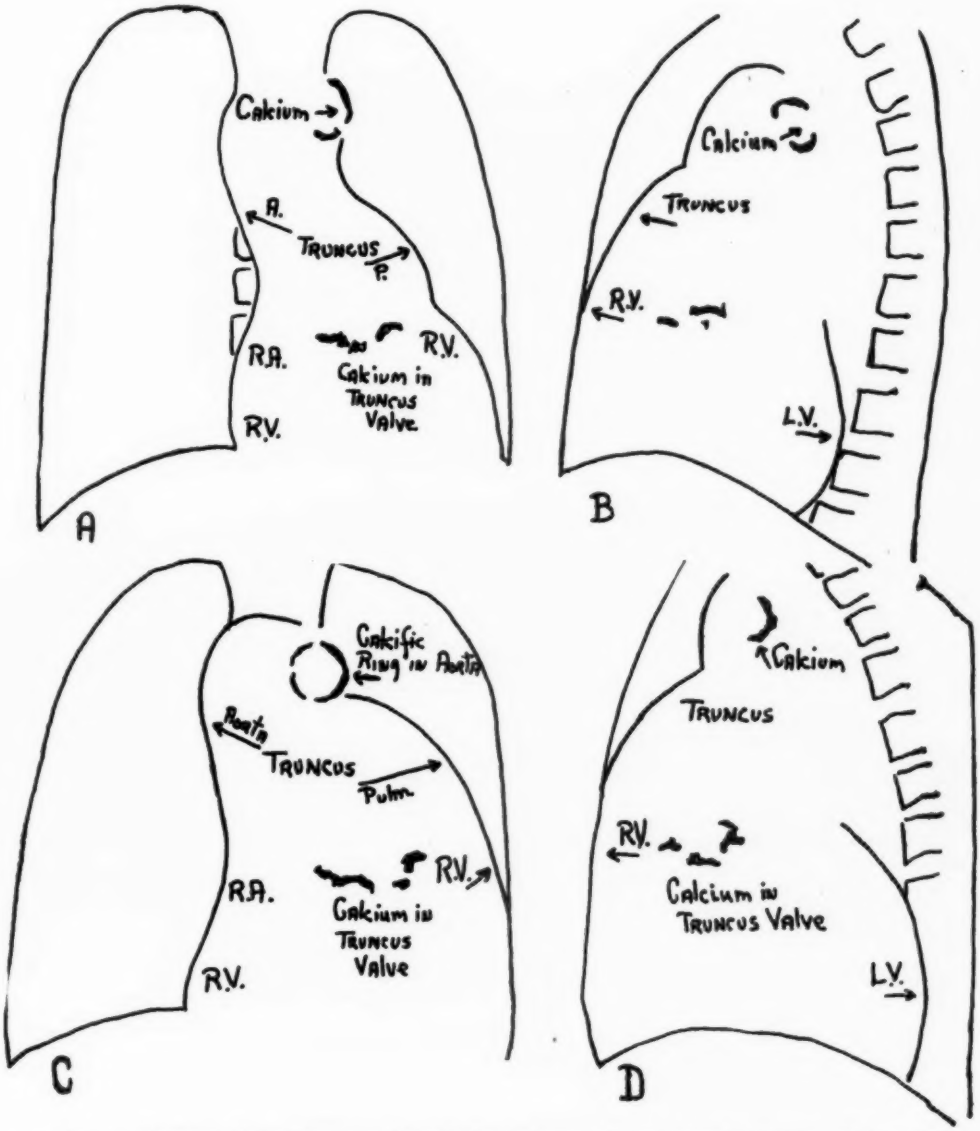

Fig. 1.—Diagram illustrating the identifiable features of the roentgenograms. R.A., right atrium; R.V., right ventricle; L.V., left ventricle; A., aorta; P., pulmonary artery.

Physical Examination: On admission to the hospital the patient's temperature was 97° F., her pulse rate 78, and blood pressure reading 110/60 in both arms. She had extreme cyanosis of the mucous membranes, distal extremities, and nail beds. She was moderately dyspneic. Her heart had a forceful apical beat visible in the anterior axillary line in the fifth intercostal

space and a regular rhythm. The murmurs were as previously described. There were moist râles at both lung bases. The liver edge was palpable one fingerbreadth below the costal margin. There was Grade 2 pitting edema about the inner thigh and pretibial area. There was marked clubbing of the fingers and toes.

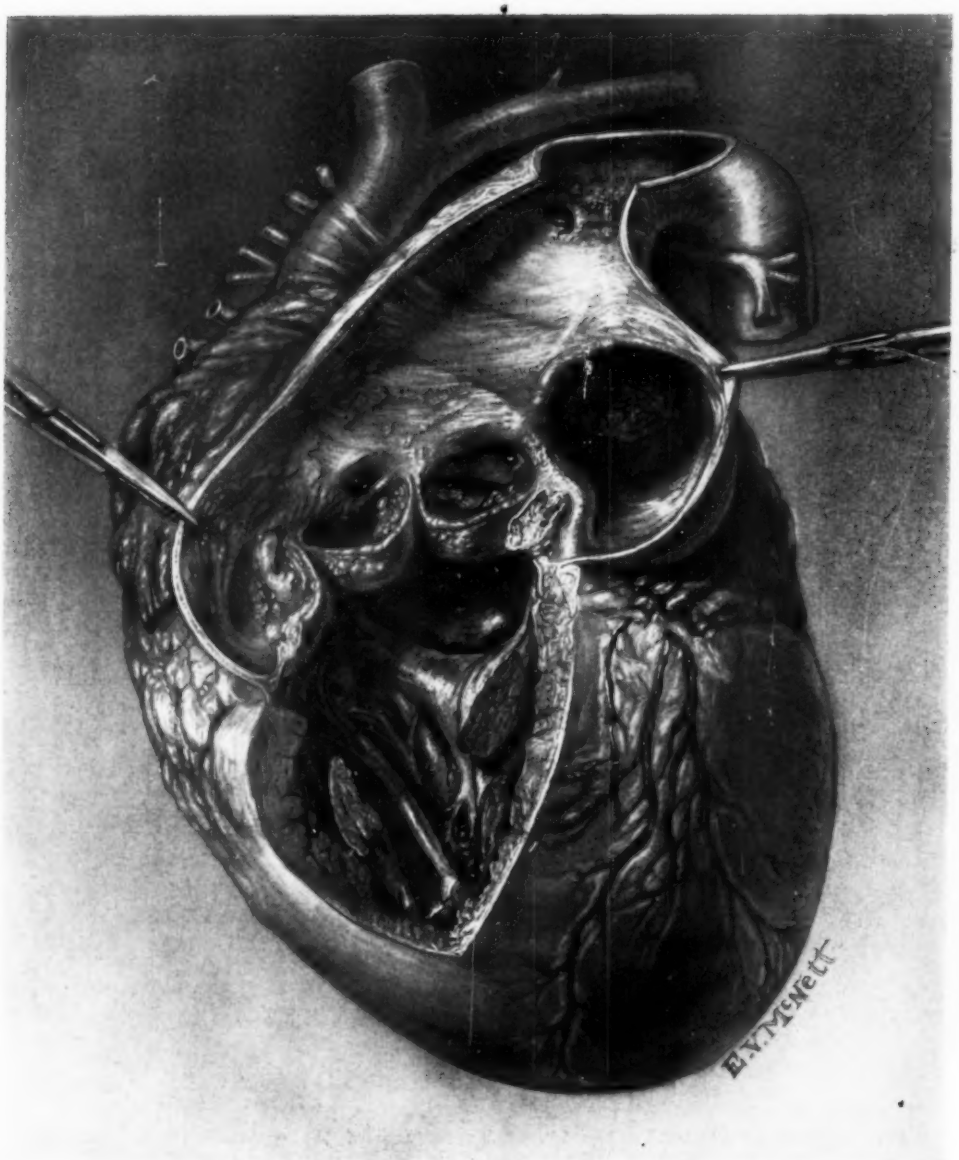

Fig. 2, *A*.—The heart as drawn looking into the right ventricle. The large interventricular septal defect is seen beneath the left anterior cusp. Opposite this cusp is the left coronary ostium. A wad of cotton is visible in the right pulmonary artery which emerges just above the left anterior cusp. Note the extensive calcific changes in the truncus valve and the ring of calcification beyond the vessel leading to the left lung.

Laboratory Studies: In August, 1939, the hemoglobin value was 20 grams; the erythrocytes numbered 5.5 million and the leucoytes, 8,000. In January, 1942, the hemoglobin value was 21 grams; the erythrocytes numbered 6.7 million; and the hematocrit equaled 61. On Jan. 30,

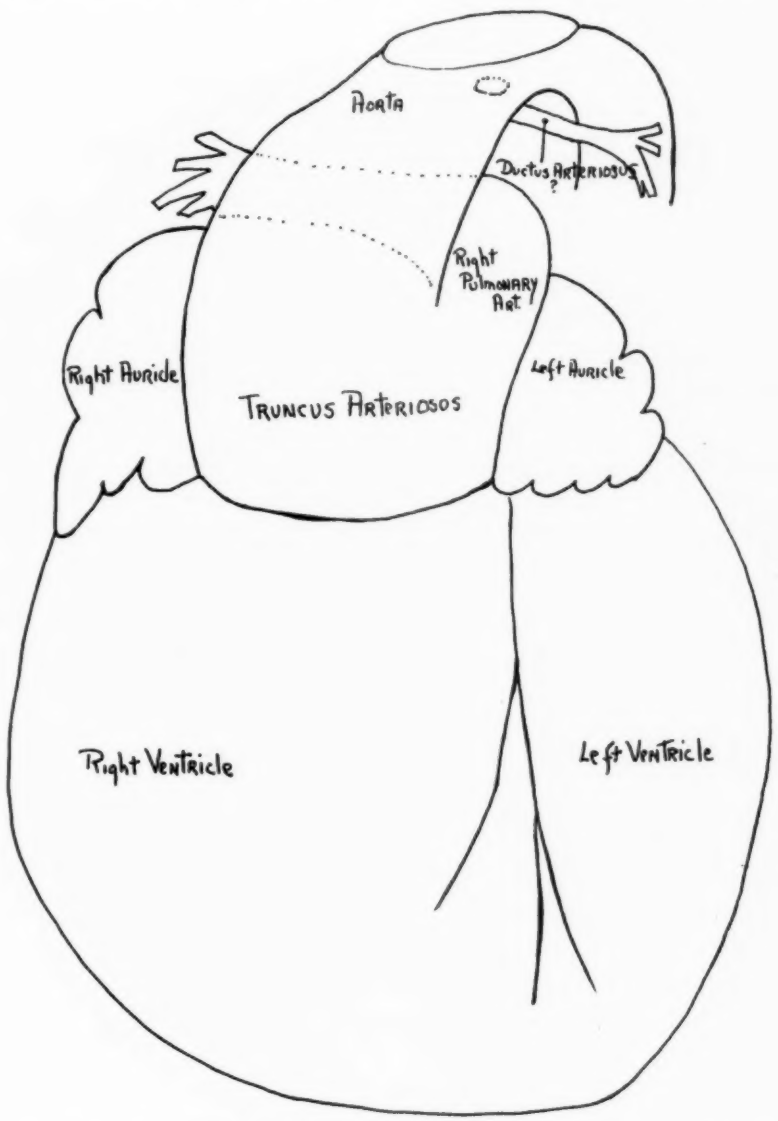

Fig. 2. *B.*—The outline of the heart is drawn to show the appearance prior to opening. For simplification the superior vena cava visible above the aorta in the drawing (Fig. 2, A) has been omitted.

1948, the hemoglobin value was 19 grams; the erythrocytes numbered 6.95 million; and the leucocytes 5,900. Blood cultures made on Jan. 30 and Feb. 1, 1948, showed no growth in ten days.

Electrocardiogram: The electrocardiograms made during 1942 to 1945 were lost. None were made during the patient's short terminal illness.

X-ray Examination: X-ray examination was performed on Jan. 30, 1948. Roentgenograms were made with the patient supine and decubitus on a litter because of her weak condition. The interpretation by Dr. E. L. Lane was as follows: Fluoroscopy reveals enormous enlargement of the heart to the left superiorly due, chiefly, to right ventricular hypertrophy. The left ventricle is enlarged posteriorly. Poor aeration exists in the left lung which is about 50 per cent displaced by the cardiac enlargement. There is no "hilar dance." The roentgenograms (Fig. 1, *C* and *D*) confirm the fluoroscopic findings. The right border of the aorta goes unusually far to the right of the mediastinum suggesting an overriding aorta. The aorta impresses the esophagus from the normal side. There is a ring of calcification in the aortic arch and calcification in the heart suggesting that seen in the mitral valve.

The diagnosis was congenital heart disease with decompensation, suggesting chiefly, an interventricular septal defect with overriding aorta and unusual enlargement of the right ventricle. The congenital defect is probably a mixture and not a classical syndrome.

Course: The patient was given oxygen intranasally, a low-salt acid ash diet, 0.1 mg. digitoxin daily, 1 Gm. ammonium chloride four times a day, and 2 c.c. Mercuhydrin (only one injection given). She showed slight improvement during the first two days following admission, but on the third day she rapidly became worse, lapsed into coma, and died that evening (Feb. 1, 1948). The clinical diagnosis was congenital heart disease.

Post-Mortem Examination: The body was that of a fairly well-developed 35-year-old white woman measuring 160 centimeters in height and weighing an estimated 60 kilograms. There was marked cyanosis of the mucous membranes, palpebral conjunctivae, and nail beds, and advanced clubbing of the fingers and toes. The lower thighs and legs showed pitting edema. Neither pleural cavity contained an excess amount of fluid, and the pleural surfaces were free of adhesions. The pericardium contained about 60 c.c. of thin, yellow fluid.

The heart (Fig. 2) weighed 685 grams and, as observed in situ, it extended for the most part into the left thoracic cavity, with little encroachment on the right lung. The right atrium and right ventricle were most prominent anteriorly. The left atrium and left ventricle bulged posteriorly into the left thoracic cavity. The transverse diameter of the heart measured 14 cm., the vertical diameter 12.5 cm., and the anteroposterior diameter in the left thoracic cavity 16 centimeters. It was estimated that cardiac enlargement reduced the potential lung space about 40 per cent. The apex was rounded and directed to the left. The auricles were in normal relation to the other chambers. From the base of the heart a single efferent trunk emerged. The epicardium was thin, smooth, and glistening. There were purpuric spots over the right ventricle, the largest measuring 0.3 centimeter. The diffusely dark-red myocardium showed marked hypertrophy, measuring 1.4 cm. in the left and 1.6 cm. in the right ventricle. All chambers were dilated. The myocardium of the right atrium was hypertrophied, varying in thickness from 0.2 to 0.4 centimeter. The foramen ovale was anatomically open but functionally closed. The superior and inferior vena cava and the coronary vein entered the right atrium in the usual manner. The right ventricle was both dilated and hypertrophied, the chamber measuring about 9 cm. in greatest vertical diameter and 6.5 cm. in greatest horizontal diameter. There was a Y-shaped muscular structure beneath an interventricular septal defect, having an underdeveloped tricuspid ledge and a relatively large trabecula septomarginalis and crista supraventricularis ending at the base of the septum beneath the truncus. The septal defect was bounded superiorly by the inferior border of the left anterior cusp of the truncus. It measured 2.8 cm. in horizontal and 1.5 cm. in greatest vertical diameter. The medial tricuspid leaflet was very small and was attached to the papillary muscle of Lancisi. The circumference of the tricuspid valve was 10.5 centimeters.

The orifice of the solitary trunk measured 10.3 cm. in circumference. It took origin from the right ventricle and was connected with the left ventricle via the septal defect. It was equipped with three cusps of equal size, two anterior and one posterior. The leaflets were markedly thickened and distorted by irregular, patchy, calcific plaques. The commissures were neither widened nor adherent. The left coronary ostium arose opposite the anterior portion of the left anterior cusp; the right, opposite the left lateral portion of the posterior cusp. These slightly thickened vessels followed the usual distribution over the ventricular surface. On the left lateral aspect of the common truncus, about 2.7 cm. above the truncus valve, the right pulmonary artery emerged. It circled the aorta posteriorly to enter the hilum of the right lung in a normal manner. The

circumference of this right pulmonary artery at its origin was 6 cm., while the aorta at this point measured 8.5 centimeters. Thereafter, the aorta followed its usual course. The exact origin and course of the brachiocephalic trunks were not known, as the crest of the aortic arch was cut away during removal of the heart and lungs. In the inferior midportion of the arch, 4 cm. beyond the branching of the right pulmonary artery, a small efferent vessel 0.6 cm. in diameter was noted; this coursed into the anterosuperior portion of the left pulmonary hilum, representing the only distinguishable arterial supply to the left lung. The recurrent laryngeal nerve passed under the aorta to the left of this vessel, and just beyond its origin the aorta was constricted and thickened by an irregular calcific ring 1.2 cm. in width. Proximal and distal to this point the aorta showed only a few slightly raised yellow plaques. Anatomically, it appeared that this vessel might represent an enlarged bronchial artery or a ductus arteriosus. No other possible remnant of a ductus arteriosus or left pulmonary artery was found. The course and distribution of the descending aorta was not unusual. The left atrial wall was not hypertrophied and the chamber only slightly dilated. The pulmonary veins entered in a normal manner. The mitral valve measured 9.6 cm. in circumference and did not appear unusual. The left ventricle was markedly dilated, measuring 9 cm. in greatest verticle diameter and 8 cm. in greatest horizontal diameter. The only exit was through the interventricular septal defect.

The lungs showed congestion and edema, the left weighing 300 grams and the right 425 grams. The abdominal organs were not remarkable except for chronic passive congestion. A small intramural leiomyoma of the uterus and mesothelial cysts of the right perirenal tissue were noted.

The anatomical diagnosis was congenital malformation of the heart (persistent truncus arteriosus communis; anatomically open, functionally closed foramen ovale; interventricular septal defect; chronic valvulitis, truncus valve; absence of the left pulmonary artery with enlarged bronchial artery or patent ductus arteriosus); dilatation and hypertrophy right auricle, right ventricle, and left ventricle; punctate subepicardial hemorrhages; chronic passive congestion in the lungs, liver, spleen, kidneys, and gastrointestinal tract; leiomyoma of the uterus; mesothelial cysts, right perirenal tissue.

DISCUSSION

This case is an example of true "partial" common truncus (Type IV) in which one of the pulmonary arteries has failed to developed or regressed and the blood supply to the dependent lung is furnished by a collateral vessel. In this case the collateral vessel was either a persistent ductus arteriosus or a superior bronchial artery. The presence of the calcified ring at a point of narrowing of the aorta and the relationship to the left recurrent laryngeal nerve would suggest a persistent ductus arteriosus. After review of the available literature it appears that this patient is the third of this type to be reported (Table I).

All patients with persistent truncus arteriosus previously described were studied in an attempt to discover any further distinctive clinicopathological features. It seemed most practical to separate the variations according to the pulmonary blood supply. The first four types are unquestionable examples of true persistent truncus. Examples of the fifth type (except where four cusps were present in two of the patients) are not absolutely proved in some instances, even though no trace of sixth arch structures or only a possible patent ductus arteriosus was found.

There were no frequently recurring noncardiac anomalies associated with any of the types. Roentgenological study of instances of Type V in children indicates that there is an absence of the normal pulmonary hilar "comma" shadow, absence of the fullness of the pulmonary conus, and, in films exposed with the subject in the left anterior oblique position, a shelflike extension of the right ventricle from the aorta to the anterior chest wall.[11,23,27] However, in a patient with two pulmonary arteries (Type II) these vessels were prominent and a "hilar"

dance was seen.[12] In our patient the hilar "comma" was present on the right, but there was the suggestion of a smaller pulmonary artery shadow on the left hilum. Marked enlargement of the cardiac silhouette was noted to the left superiorly (a different picture from that seen in truncus arteriosus in infants[23,27]). The calcification in the truncus valve visible in x-ray films and the ring of calcification in the aortic arch were noteworthy findings.

In previously recorded cases, cyanosis was universally present. It was most intense in patients of Type V and usually moderate in patients of the other types. Percentage of survival beyond the second year of life in patients with truncus without pulmonary arteries would seem to be similar to that of patients with pulmonary arteries. The actual period of survival in patients of all types is probably not as great as indicated, since many patients dying before the second year of life are undoubtedly not reported. The degree of development of the aorticopulmonary septum does not appear to be as important a factor in survival as the size of the pulmonary arteries, or the size of the collateral vessels, when the pulmonary arteries are absent.

SUMMARY

A case of truncus arteriosus communis persistens (Type IV) in a patient who survived to the thirty-fifth year of life is presented, along with a tabular review of previously reported cases. The varying roentgenological findings in persons with different types of this malformation and in the adult as distinct from the infant are mentioned. The sufficiency of the pulmonary circulation is suggested as an important factor in survival.

I wish to express my appreciation to Dr. R. Philip Custer for his valuable criticism and advice in the writing of this paper.

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AN UNUSUAL CARDIAC ANOMALY

A Report of Two Cases

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TWO subjects encountered in a series of routine autopsies present almost identical combinations of several individually rare anomalies. Each had a three-chambered heart with two atria, a common arterial trunk and a common brachiocephalic trunk.

Maude Abbott[1] in her analysis of 1000 cases of congenital heart disease reported only 13 cases of cor triloculare biatriatum; 21, of persistent truncus arteriosus; and 2, of common brachiocephalic trunk. None of these defects occurred in the combination mentioned above. Since then, various reports of these individual abnormalities have appeared in the literature but none with all in the same subject. Mehta and Hewlett[2] reported a case of cor triloculare biatriatum with a persistent truncus arteriosus. In their case, however, there was no common brachiocephalic trunk and the pulmonary circulation was not clearly traced post mortem.

CASE REPORTS

Case 1.—This white female infant was apparently normal at birth, weighing 6 pounds, 7 ounces. Both gestation and delivery were normal. No cyanosis was observed and no cardiac murmurs heard. Rather suddenly on the fifth day the infant's skin took on a bluish-grey cyanotic hue associated with vigorous crying. Her respirations became rapid, then labored and finally shallow. Her color did not improve with oxygen and she died in less than two hours.

Autopsy was performed nine hours after death. The body was that of a well-developed female infant which, except for marked cyanosis and post-mortem lividity, was normal externally. The thymus was normal and the lungs showed marked congestion but no appreciable edema.

The abnormalities noted in the heart are shown in the accompanying illustration. A common single arterial trunk arose from a single ventricle with three well-formed semilunar valves. The origin of the left coronary artery was demonstrated in the left posterior sinus of the truncus. The right coronary artery arose from the innominate artery and ended in the right atrioventricular groove, probably representing an atresic aorta.

A short distance above the semilunar valves the common truncus arteriosus gave origin to right and left pulmonary arteries. The main trunk continued as the ascending aorta and from its arch gave off a common brachiocephalic trunk which in turn terminated in the innominate, left common carotid, and left subclavian arteries. The remainder of the aorta was normal.

Both pulmonary veins emptied into a small left atrium and both the superior and inferior vena cava emptied into a dilated right atrium. The small left atrium communicated with the right atrium through a slit-like septal defect 0.6 cm. long protected by a well-formed flap on the right side. The left atrium did not communicate with the ventricle. A well-formed tricuspid valve separated the right atrium from the ventricle. The ventricle was dilated and its wall hypertrophied.

The abdominal viscera were normal except for venous congestion.

Case 2.—Baby R., a white girl, was born by a normal delivery, the second child in the family. The history of the parents was non-contributory.

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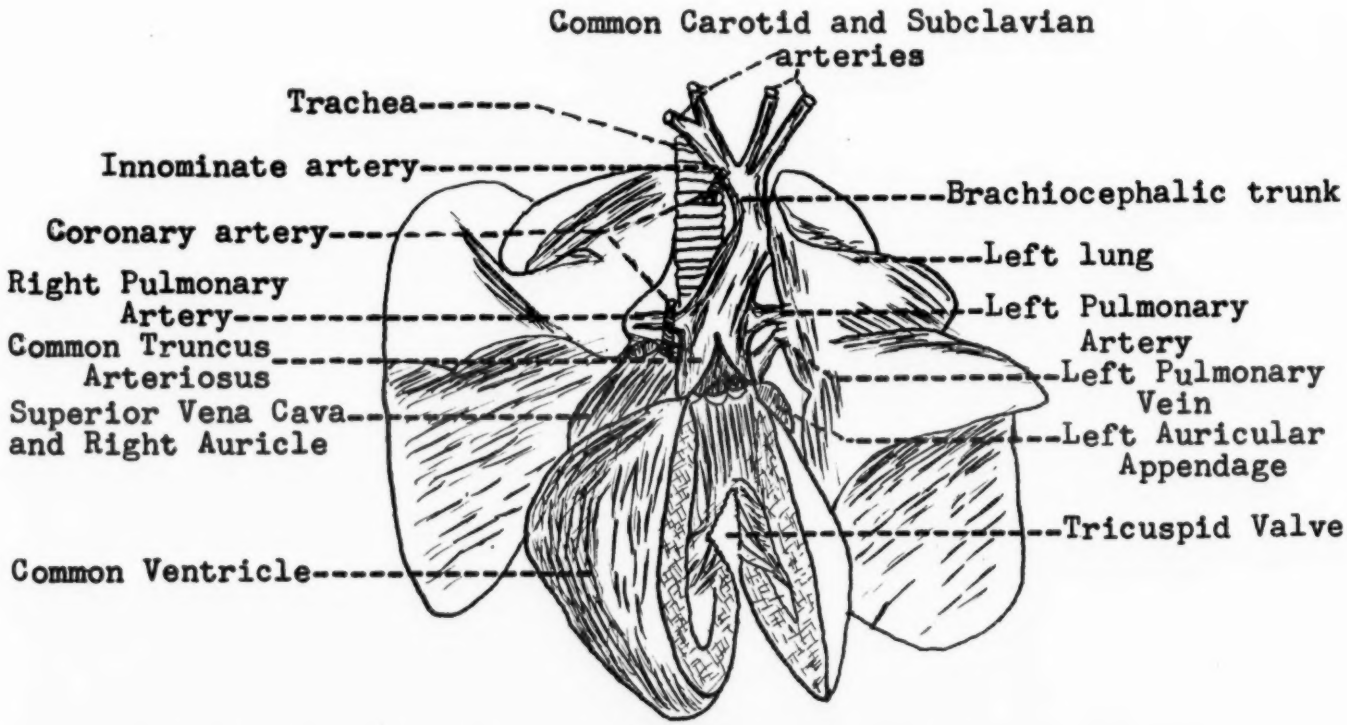

Fig. 1.—Cor triloculare biatriatum with common truncus arteriosus, brachiocephalic trunk, and patent foramen ovale.

The child appeared normal at birth but on the third day became cyanotic. Despite vigorous attempts at resuscitation the cyanosis was progressive and the infant ceased to breathe on the afternoon of the third postnatal day.

At autopsy the infant was well developed and possessed no external abnormalities except a marked cyanosis.

As in Case 1 the positive findings were confined to the heart which was enlarged. It weighed 33 grams and several subpericardial petechial hemorrhages were present.

The gross appearance of the heart was, in all respects, an exact replica of that of Case 1. As in Case 1 a single ventricle with a three-valved common arterial trunk was present. The two small pulmonary arteries and the common brachiocephalic trunk arose from the truncus arteriosus at the identical positions noted in Case 1. A physiologically patent foramen ovale was also present and a single coronary artery arising in the common brachiocephalic trunk divided into two branches at the base of the heart.

DISCUSSION

The cause of a single ventricle is well-explained in all standard texts of embryological anatomy. It is apparently due to a lack of development of the membranous down-growth from the interatrial septum and the right side of the aortic root along with a failure of growth of the fleshy part of the interventricular septum from the apex of the common ventricle. This commonly occurs about the end of the fourth week in utero.

Incomplete development of the septum primum and septum secundum in the common atrium during the seventh week of intra-uterine life is responsible for the physiologically patent foramen ovale.

In most cases of true persistent truncus arteriosus four semilunar valves are described. In the two cases here presented only three valves were found. In these two cases the single coronary artery arising from the common brachiocephalic trunk probably represents the atresic aorta and the single large vessel, the pulmonary artery. If this is so, these cases are not examples of true persistent truncus arteriosus. If the single coronary artery represents the aorta, then the portion of the large vessel between the common brachiocephalic trunk and the origin of the right and left pulmonary arteries may well represent a large, persistent ductus arteriosus.

The physiology in these cases is obviously one of complete mixing of arterial and venous blood as is seen in the reptile heart. The condition is theoretically compatible with life at a very limited level of activity. Neither mother had German measles during pregnancy.

SUMMARY

Two identical cases of congenital heart disease are reported. Each presented a cor triloculare biatriatum with a common truncus arteriosus and common brachiocephalic trunk and with an unusual coronary anomaly. Both were white female infants, five and three days old, respectively. This is a rare combination of cardiac anomalies. The developmental defects are discussed briefly.

The authors wish to thank Doctor George Sumner and Doctor Kenneth McAlpine, respectively, for permission to publish these two cases.

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ACUTE CORONARY INSUFFICIENCY PATTERN FOLLOWING INTRAVENOUS ERGOTAMINE STUDIES

Report of a Case

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United States Army†

THIS case presentation is prompted by the continued popularity of the intravenous use of ergotamine tartrate to determine whether or not certain abnormal changes in the T waves are due to an autonomic nervous system imbalance. Recent reports[1] indicate a trend in the use of a related oxytocic drug, ergonovine, in the precipitation of coronary insufficiency for diagnostic purposes. Scherf and Schlachman,[2] in their studies with ergotamine tartrate and dihydroergotamine, adequately pointed out the possible dangers involved in the routine use of this apparently under-estimated drug. The use of these drugs, therefore, in patients with conclusive clinical and/or electrocardiographic evidences of coronary insufficiency is not, in our opinion, warranted unless the possible consequences are fully appreciated.

Ergotamine tartrate has its most useful application in the evaluation of subjective symptoms suggestive of coronary insufficiency. Here, where an erroneous diagnosis of cardiovascular disease could well precipitate a cardiac neurosis, any impersonal and objective data, including the effect of ergotamine, which could be used in the reassurance of these patients, would have a psychotherapeutic, if not diagnostic, value. Accordingly, intravenous ergotamine tartrate (Gynergen) in the standard dosage of 0.5 mg. (1 c.c.) has been employed in our Cardiac Clinic without incident in more than fifty subjects and has proved of value when correlated with clinical findings. The single untoward incident herein reported demonstrated that the drug is not without danger and emphasizes the need for caution and the proper selection of subjects.

CASE REPORT

A 46-year-old, white, male Army Captain was admitted to Oliver General Hospital on May 6, 1949, with a history of having been in good health until Feb. 3, 1949. At this time he ran a short distance and about one minute after cessation of activity experienced a severe, substernal pain, sharp in nature and radiating down both arms to the elbow. This occurred at approximately 8:00 P. M. and about one and one-half hours after dinner. The pain lasted about ten minutes and was not accompanied by shortness of breath or other symptoms. Several minutes later, when he arose to answer the phone, a similar episode of pain occurred. There was no further recurrence although the patient in the next two days attended a dance and also walked five miles without difficulty. Four days after this episode of pain an electrocardiogram was taken which revealed T waves in Lead I of low amplitude, averaging 1 mm. or less, but otherwise it was not

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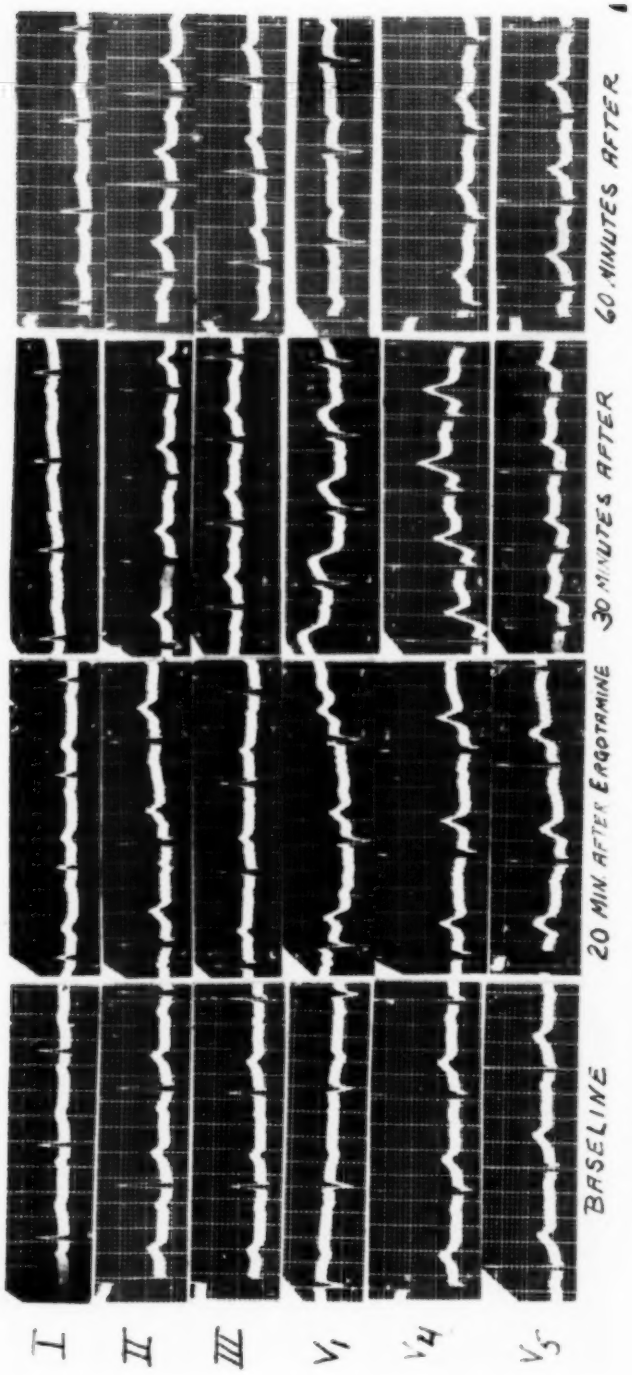
I
II
III
V1
V4
V5
BASELINE
20 MIN. AFTER ERGOTAMINE
30 MINUTES AFTER
60 MINUTES AFTER

Fig. 1.

unusual. He was admitted to a station hospital on Feb. 8, 1949, for observation and on Feb. 10, 1949, the patient had another similar episode of pain and his blood pressure dropped to 80/60 mm. of mercury. The patient was placed in an oxygen tent, although nitroglycerine produced prompt relief and the patient had no further difficulty. Treatment consisted of bed rest and careful observation, but the patient experienced no further episodes of significance and he was transferred to Oliver General Hospital on May 6, 1949, as a possible coronary occlusion patient.

On admission the patient was asymptomatic and afebrile. An electrocardiogram revealed only the persistent low T_1. The patient continued to have vague left shoulder and arm aches unrelated to activity and not characteristically cardiac in nature. He also had a history of old duodenal ulcer which investigation revealed to be inactive with residual deformity of the duodenal cap.

Review of previous electrocardiograms revealed the T wave in Lead I to have varied from mild inversion to upright with the highest amplitude averaging 1 millimeter. Routine tracing following admission to Oliver General Hospital showed only the low T waves in Lead I. Master's exercise tolerance test on May 17, 1949, was normal. Because of the vagueness of many of the patient's pains and the presence of possible increased vagal activity, plus manifestations of gaseous distention and a spastic colon, further evaluation was felt indicated in regard to the electrocardiographic findings. Consequently on May 20, 1949, the patient was given 0.5 mg. of ergotamine tartrate, intravenously, with the following clinical episode and electrocardiographic changes: Fifteen to twenty minutes following injection the patient began to complain of severe right parasternal pain, radiating to both shoulders, arms and hands. The blood pressure fell slightly from 139/84 mm. Hg to 120/74 mm. of mercury. The patient became cool, clammy, perspired profusely, and tossed about constantly. He was given $\frac{1}{75}$ gr. of atropine intravenously with relief of the pain within 30 to 60 seconds. Tracings were taken during the episode and at 30 and 60 minutes following the injection of the ergotamine. The patient described this episode as being similar to his original attack, but of a much greater severity. An electrocardiogram taken at the height of the attack revealed some lowering of the voltage of the QRS complex in Lead I, with flattening of the S-T segments in Leads I, II and III. In the precordial leads there was an increase in amplitude of the R wave in Lead V_1 with the T wave in Lead V_1 changing from a negative to an upright position of good amplitude. Lead V_4 revealed an increase in amplitude and peaking of the T waves with flattening of the S-T segments and a tendency to depression of the S-T segments. At this time the patient was given $\frac{1}{75}$ gr. of atropine intravenously which relieved his pain. Thirty minutes after ergotamine the QRS complex in Lead I was of an amplitude similar to the baseline, as were the T waves. Leads II and III had reverted to the baseline pattern. The T wave in Lead V_1 had rounded off, as compared to the 20-minute tracing but was still upright and a somewhat deeper S wave was noted at this time as compared to the 20-minute tracing. There was more definite depression of the S-T segment in Lead V_4. The S-T segments in V_5 had also become more flattened and were depressed an average of 1 millimeter. Sixty minutes following ergotamine, the tracing had reverted to a baseline status entirely, although the T waves in Lead I were of slightly better appearance and the S wave in V_1 was deeper (Fig. 1).

The patient returned to his ward feeling well, but approximately two to three hours later, after a few bites of dinner, experienced another severe episode of angina-like pain. The patient appeared apprehensive with a fast, thready pulse and was perspiring about the face and scalp. One $\frac{1}{100}$ gr. of nitroglycerine produced prompt relief and the patient was placed at bed rest. This episode occurred at approximately 5:30 in the afternoon. An electrocardiogram taken about fifteen minutes following this episode showed only slight depression of the S-T segments in Leads V_4 and V_5. An hour later he experienced another attack which was less severe and he was given papaverine, 3 gr. orally, and placed on this drug every four hours. He again was given nitroglycerine ($\frac{1}{100}$ gr.) with immediate relief. It was decided to place the patient in an oxygen tent overnight. He had further attacks requiring nitroglycerine at 8:30 in the evening and again at 1:00 on the morning of May 21. He felt tired and the midsternal area was sore the following day, but no further pain occurred and the oxygen tent was discontinued. The patient had a poor appetite with mild nausea but was otherwise asymptomatic. Since the night of May 20-21 the patient has had no further episodes of acute pain to date, but has complained intermittently of soreness about the left shoulder girdle and both wrists.

COMMENT

The cause and effect relationship between the administration of ergotamine and the acute symptoms produced, seems apparent. Likewise the reproduction of the type of pain which brought the patient to the hospital is interpreted to indicate that the spontaneous and the reproduced mechanisms are identical. Although the mechanism of the action of ergotamine is not entirely clear, in this case the action of the drug on the coronary circulation would seem to be through vagal hyperactivity. This hypothesis is substantiated by the fact that an antagonistic drug, atropine, given intravenously, consistently produced relief of pain within 30 to 45 seconds. Further, in test animals acetylcholine is reported[3] to first increase, then decrease, coronary blood flow. It would seem logical to assume that exaggerated vagal action could be due to a potentially overactive vagus released from compensatory inhibition by the sympathicolytic effect of the drug.

The period of maximum sympathicolytic effect, following intravenous ergotamine has been generally accepted as occurring 30 minutes after injection.[4,5] In this patient definite effects appeared within fifteen minutes, an observation noted in other reports.[1]

SUMMARY

A report has been presented which emphasizes the need for caution in the use of ergotamine tartrate for the evaluation of autonomic nervous system influences on the electrocardiogram. A possible mode of action to explain the mechanism by which this acute coronary insufficiency pattern was precipitated, as a result of coronary vasoconstriction, is suggested. The relationship between the recurrent episodes of angina-like pain and the intravenous use of ergotamine is not determined at this time, although a similar episode of ten hours duration was noted in one of Scherf's[2] patients and substernal pain of nine hours duration following intramuscular injection has also been recorded.[6]

CONCLUSIONS

(1) The use of ergotamine tartrate intravenously is not without hazard.

(2) The proper selection of cases is mandatory.

(3) Nitroglycerine, atropine, or oxygen should be available during the performance of a test.

(4) The use of ergotamine tartrate is contraindicated in patients with conclusive clinical and/or electrocardiographic evidence of coronary insufficiency.

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Editorial

NATIONAL CONFERENCE ON CARDIOVASCULAR DISEASES

THERE was held in Washington, January 18 to 20, 1950, a National Conference on Cardiovascular Diseases. This was sponsored by the American Heart Association and the National Heart Institute. The purposes of the Conference were stated as follows:

> To investigate, define and develop immediate and long-range programs designed to meet the problems of research, education and community service posed by diseases of the heart and circulation, and to coordinate the efforts of all groups concerned with these problems with a view to gaining the most effective use of their resources for all the members of the community.

This was, in many ways, an unusual conference although not unique. There was a time, not so long ago, when a conference dealing with cardiovascular diseases would be confined only to the medical profession. But, through the influence of a broadening solicitude for human well-being, other social disciplines have been taken into the general concept of human happiness. The initiation of this concept is hard to date accurately, but, through devastation and man's brutality to man, there arose the ideology of the United Nations. Therein is a dream which, some day in the fullness of time, may come true. But apart from the low strivings for world conquest with a narrow belief in human dignity, there has evolved the practical concept of UNESCO and the World Health Organization.

The essence of the present progress of Medicine is toward the total welfare of man. This is well demonstrated by the International Congress for Mental Health in London in 1949. Here there was arranged a well-planned and coordinated program which included contributions toward a common end from physicians, pediatricians, sociologists, educationists, psychologists, psychiatrists, anthropologists, and all disciplines which could contribute to the welfare of mankind within the orbit of the general thesis of the congress.

So was the conference in Washington. It must be obvious that the first section should lay the basis, describing, in simple understandable language, the problems of the cardiovascular diseases, and outline the research disciplines and policies which would carry onward fundamental truth toward the solution of these many ills.

But this aspect of the conference might be taken as the primary or introductory part. In the less medical spheres lay the real essence of the conference. These represented the contribution which the social sciences and education can make to broaden the rather narrow concept held by many physicians who seem to believe that the beginning and end of the relief of cardiovascular disease rests on traditional therapy.

Section II dealt with community services, lay education and prevention, case-finding and epidemiology, treatment and management services and facilities, and integration of community services and facilities. It opened a wide horizon where many existing agencies could contribute vastly toward the solution and mitigation of this foremost cause of human misery and disability. This section made a distinct contribution to the whole problem and, by inference, indicated the responsibility of Section III.

This section surveyed the educational standards of physicians, nurses, social workers, and teachers, and here lay the challenge of the whole conference. This can be summarized in a few words: There are many unsolved problems in our knowledge of the cardiovascular diseases. There is a problem for the physicians with their experimental methods, for the epidemiologists and lay educationists, and for the professional educators. Finally, what was consistently and persistently emphasized by all sections, was the important and even urgent necessity of integrating all efforts to the so'ution and amelioration of the cardiovascular diseases within the over-all realm of the community health and social services.

May the endeavors of this conference bring wide and beneficient help to an urgent problem!

J.C.M.

Announcements

THE SOCIETY FOR VASCULAR SURGERY

FOURTH ANNUAL MEETING

June 25, 1950

Fairmont Hotel, Terrace Room San Francisco, California

Preliminary Program

President: Daniel C. Elkin

Intravenous Agglutination of Erythrocytes (Sludged Blood) in Trauma
W. G. Bigelow, M.D.

Surgical Management of Secondary Hypersplenism
Jere Lord, Jr., M.D.

The Management of Popliteal Aneurysms
J. M. Janes, M.D.

Experimental Studies of the Frozen Homologous Aortic Graft
Ralph A. Deterling, Jr., M.D., C. C. Coleman, Jr., M.D., and Mary Parshley, Ph.D

Some Experimental Aspects of Coarctation of the Aorta
Frank Gerbode, M.D.

The Effect of Vasodilator Drugs on the Circulation of the Extremities
Daniel C. Elkin, M.D., President's Address

Raynaud's Syndrome: A Clinical Study of Criteria for Prognosis
Frederick Coller, M.D., and Alexander Blain III, M.D.

An Evaluation of the Deep Leg Veins Following Thrombophlebitis
Josephus C. Luke, M.D.

Division of the Popliteal Vein in Deep Venous Insufficiency of the Lower Extremities
Geza deTakats, M.D., and G. W. Graupner, M.D.

Acute Massive Occlusion of the Venous System of the Lower Extremities
J. Ross Veal, M.D.

Ambulatory Venous Pressure Studies in the Postphlebitic and Other Disease States
Paul DeCamp, M.D., J. A. Ward, Jr., M.D., R. J. Schramel, M.D., N. D. Feibelman, M.D., and Alton Ochsner, M.D.

Experiences With Ligation and Heparin in the Prevention of Pulmonary Emboli
Isador Ravdin, M.D., and Charles K. Kirby, M.D.

THE PAPERS WILL BE OPEN FOR GENERAL DISCUSSION

THE SIXTH ANNUAL CONGRESS OF THE BRAZILIAN SOCIETY OF CARDIOLOGY

The Sixth Annual Congress of the Brazilian Society of Cardiology was held from July 5 to 10, 1949, in the city of Recife, Pernambuco.

The next meeting will take place on the same dates in the Cassino Hotel Quitandinha, near Petropolis, in the state of Rio de Janeiro.

The following officers were elected for the 1949-50 term:

President	Dr. Arnaldo Marques
Vice-President	Dr. Luiz Capriglione
Secretary-General	Dr. Antonio Araujo Villela
Second Secretary	Dr. Bernardino Tranchesi
Treasurer	Dr. Gilberto Surreaux Strunck
Director of Archives	Dr. Jairo Ramos

The under-noted are the local representatives of the Society:

Dr. Gilberto Surreaux Strunck	Rio de Janeiro
Dr. Bernardino Tranchesi	São Paulo
Dr. Jose Moreira Ferreira	Bahia
Dr. Arnaldo Marques	Pernambuco
Dr. Rubens Maciel	Rio Grande do Sul
Dr. Eugenio Lopes	Paraná
Dr. Maria do Carmo Sarmento de Carvalho	Pará
Dr. Caio Benjamin Dias	Minas Gereis